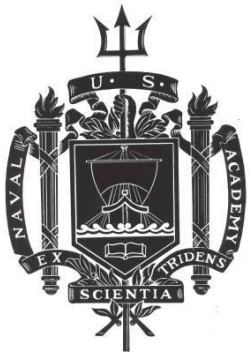
A TRIDENT SCHOLAR PROJECT REPORT

NO. 464

Assessment of Genetic Screening in the Military

by

Midshipman 1/C John Joseph Brough III, USN



UNITED STATES NAVAL ACADEMY
ANNAPOLIS, MARYLAND

USNA-1531-2

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE *(DD-MM-YYYY)*	**2. REPORT TYPE**	**3. DATES COVERED** *(From - To)*
05-21-18		

4. TITLE AND SUBTITLE
Assessment of Genetic Screening in the Military

5a. CONTRACT NUMBER

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Brough, John J.

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Naval Academy
Annapolis, MD 21402

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)
Trident Scholar Report no. 464 (2018)

12. DISTRIBUTION / AVAILABILITY STATEMENT

This document has been approved for public release; its distribution is UNLIMITED.

13. SUPPLEMENTARY NOTES

14. ABSTRACT

The goal of this project was to undertake a cost-benefit analysis of genetic testing in military populations. We weighed the costs of genetic testing against the likelihood of saving lives of military recruits with undetected, potentially life-threatening genetic conditions. Large genomic databases of asymptomatic populations were used to analyze the effect that genetic screening for hypertrophic cardiomyopathy (HCM, the most common cause of sudden cardiac death) would have on the military. A database containing known pathogenic variants was used as a training set to build logistic regression models that predicted the pathogenicity of genomic variants in two genes known to cause HCM. Our cost-benefit analysis was based, in part, on the frequency of the identified pathogenic variants, as well as their likelihood of causing disease. We compared the costs and benefits of genetic screening to non-genetic physiological tests or no tests at all. We also distributed a survey to the United States Naval Academy to assess the attitudes regarding genetic screening in the military. We conclude that genetic screening with a follow-up echocardiogram for the detection of HCM is a viable and cost-effective option if a microarray genetic test is used. We find that individuals in the military view genetic testing as a viable medical test, but are concerned about the use of genetic screening to make employment decisions.

15. SUBJECT TERMS
Genetic screening, hypertrophic cardiomyopathy, population genetics, genetic testing, medical testing

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**		198	**19b. TELEPHONE NUMBER** *(include area code)*

U.S.N.A. --- Trident Scholar project report; no. 464 (2018)

ASSESSMENT OF GENETIC SCREENING IN THE MILITARY

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USNA-1531-2

Assessment of Genetic Screening in the Military

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May 2018
Trident Scholar Report
No. 464

Abstract

The goal of this project was to undertake a cost-benefit analysis of genetic testing in military populations. We weighed the costs of genetic testing against the likelihood of saving lives of military recruits with undetected, potentially life-threatening genetic conditions. Large genomic databases of asymptomatic populations were used to analyze the effect that genetic screening for hypertrophic cardiomyopathy (HCM, the most common cause of sudden cardiac death) would have on the military. A database containing known pathogenic variants was used as a training set to build logistic regression models that predicted the pathogenicity of genomic variants in two genes known to cause HCM. Our cost-benefit analysis was based, in part, on the frequency of the identified pathogenic variants, as well as their likelihood of causing disease. We compared the costs and benefits of genetic screening to non-genetic physiological tests or no tests at all. We also distributed a survey to the United States Naval Academy to assess the attitudes regarding genetic screening in the military. We conclude that genetic screening with a follow-up echocardiogram for the detection of HCM is a viable and cost-effective option if a microarray genetic test is used. We find that individuals in the military view genetic testing as a viable medical test, but are concerned about the use of genetic screening to make employment decisions.

1 Acknowledgments

The past four years, and especially this project, have been both a struggle and a joy. The only reason I can say they have not been completely the former is because of the people that have helped me along the way.

First, I would like to thank all of those who supported me through my early years here and even before I got here. From teachers in grade school and high school that inspired and fostered my thinking and interest in science to coaches who told me never to quit, they have all in some way helped me complete this project. I'd like to thank Andrew Zhao, who helped me learn the ropes my first few years here, Dr. Isaac, who first gave me the idea to pursue a Trident in plebe year, and for Professor Teichert for being the best academic advisor I could ever have asked for. All of my professors at USNA have supported me through this, either directly or indirectly. Professor Rehill was always someone I could bounce ideas off of, Professor Lin both pushed me and instilled so much confidence in me during those intimidating times early in the chemistry major. Professor Kinter, Professor Waite, and all who have taught me throughout my time here, I can't thank you enough.

It was over two years ago that I emailed over 40 PIs at the National Institutes of Health to see if I could get a summer position there. Luckily, the Muenke lab took a chance on me. Dr. Kruszka came up with the idea of assessing genetic screening in the military, and gave me free reign on the project to work through as a Trident report. The lab was always a place I could go to and bounce ideas off of anyone, and was full of people with expert insight who were willing to teach a beginner. I'd specifically like to thank Dr. Maximilian Muenke, Dr. Paul Kruszka, Dr. Seth Berger, Mr. Don Hadley, and even Kat, Emily, Sofia, and Yonit. Of course, I can't leave out Dr. Mahim Jain, who spent hours upon hours working and talking with me about the genetics and statistics behind my project. Without him, this would be nothing.

I can't thank my USNA team enough as well. Professor Morse was always someone I could present my project to, someone who offered an expert perspective, and someone who helped me convey my project better to others. I'd like to thank Eunbi Rha (ROK forever) and the USNA engineering server operators for letting me use their servers so my computer didn't completely die of exhaustion. Professor Teichert and Professor Johnson were invaluable in getting my survey proposal through, and I can't thank them enough. I'd also like to thank the USNA Human Research Protection Program (HRPP) for so quickly moving my survey through the process. And, of course, I'd like to thank everyone who participated in the survey. Your results were invaluable to this study, and the response rate was outstanding.

It was a few months into the first semester of 1/C year that I realized I was way over my head in statistical analysis and modeling, and I would need a mathematics expert on the yard to help me. Professor McGuffey came to my rescue, and without her constant assistance and help that amounted to days out of her schedule, this would be nothing as well. She taught me R from scratch and I learned more about probabilities and statistics from her and this project that I ever imagined I would. I will remember what she taught me forever and can't thank her enough for all the effort she put into this project.

Finally, I'd like to thank my friends and family who helped me through this place. Mom, Dad, Peter, and Ginny: you all are the best. I'd like to thank LT Kalfus and Senior Chief Washa for supporting me through this project and allowing me to make trips to the NIH every week. Of course, I'm not sure if I'd be a Trident without the help of good ol' Chris Panuski. He was always someone I could go talk to back in the day. And, last but not least, I'd like to specifically thank my former roommates of 2.5 years, Matt and Stephen. Somehow they (barely) put up with my neuroticism for an extended amount of time. They will never ever in a million years read this thing, but thanks guys.

2 Project Synopsis

We provide this section as a general overview of the entire project methods, results, and conclusions. All details can be found in the rest of the report.

2.1 Introduction

Genetic testing is becoming more and more relevant to medicine. With the cost of genetic testing lowering every day, and with the clinical significance of genetic tests improving as well [1], the application of genetic testing to the military to determine diseases that may impede military service may be used. In this study, we look to determine how feasible genetic testing may be in the military by analyzing how it may be used on a single condition, hypertrophic cardiomyopathy (HCM), and also analyze what additional ideological and psychological barriers may exist in order to implement genetic screening in the military.

The most common cause of nontraumatic death in the military is sudden cardiac death (SCD) [2]. HCM is the leading cause of sudden cardiac death among young athletes, and occurs in 1 in 500 individuals [3]. The military has interest in exploring HCM for this reason. We focus our analysis on the genes MYH7 and MYBPC3, two genes which cause 80% of HCM [4].

2.2 Methods

2.2.1 Determination of Disease-Causing Variants

We explored the ClinVar database for variants that were either pathogenic/likely pathogenic, and benign/likely benign with no conflicting interpretations in the genes MYH7 and MYBPC3. Table I-1 displays the results. 90 pathogenic variants, and 346 benign variants in ClinVar for these two genes were found.

Table I-1: ClinVar Variants in MYH7 and MYBPC3

Gene	# of Benign Variants	# of Pathogenic Variants	Freq. of Benign Variants	Freq. of Pathogenic Variants
MYH7	203	44	2.52	5.55E-4
MYBPC3	143	46	2.75	9.47E-4

Because genotype-disease empirical correlation is likely incomplete, we built a logistic regression model which predicted variant pathogenicity. This model was built by using different combinations of the parameters listed below:

1. **Allele Frequency:** The frequency of the variant in gnomAD
2. **Genetic Conservation:** GERP
3. **Genetic Conservation:** Vertebrate PhyloP
4. **Combined Annotation Dependent Depletion (CADD)**

Table I-2: Top 5 Models According to AIC

Model #	Allele Frequency	Gerp	CADD	Splice Indicator	Vertebrate PhyloP	AA Change?	Conservative Change?	MYH7 Rank	MYBPC3 Rank	MYBPC3 + MYH7 Rank	Total Rank Number	Rank
46	■		■	■		■		5	4	1	10	1
122	■	■		■	■		■	11	2	3	16	2
44	■	■		■		■		4	9	4	17	3
45			■	■		■		2	10	6	18	4
110	■		■	■		■	■	10	7	2	19	5

5. **Protien consequences:** amino acid change
6. **Protien consequences:** nonconservative amino acid change
7. **Splice site pathogenicity (dbscsnv)**

We used R to run 64 different combinations of the above parameters, and determined the optimal model based on AIC. The models were ranked based on AIC in predicting variant pathogenicity in MYH7 and MYBPC3 sepearatley, and also in a combined MYH7 and MYBPC3 dataset. The top 5 models are listed in Table I-2. Black squares in Table I-2 indicate the presence of the parameter.

Leave-one-out cross-validation (LOOCV) was performed on the combined MYH7/MYBPC3 model 46 and found it to have a sensitivity of 94.4% and specificity of 99.7% for known pathogenic and known benign variants in MYH7 and MYBPC3.

A "ranked-varint list" was created based off of the results from this model, with the variants ranked in order of increasing model score, and hence increased prediction of pathogenicity. This list was used in the simulation described below to assign disease causing variants in the simulation.

2.2.2 Cost/Benefit Analysis

A cost/benefit analysis was created with an overview schematic displayed as Figure I-1. The process of the cost/benefit analysis is explained below in a step-wise manner.

1. **Simulate pathogenic variant frequencies:** In order to simulate variant frequencies as they occur in the general population, we used the gnomAD database [21] to determine how frequently pathogenic variants would occur in our simulated population of individuals. The gnomAD database was used as a surrogate of the military population due to the asymptomatic nature of both populations. The frequency of pathogenic variants in simulated populations depended in part on how

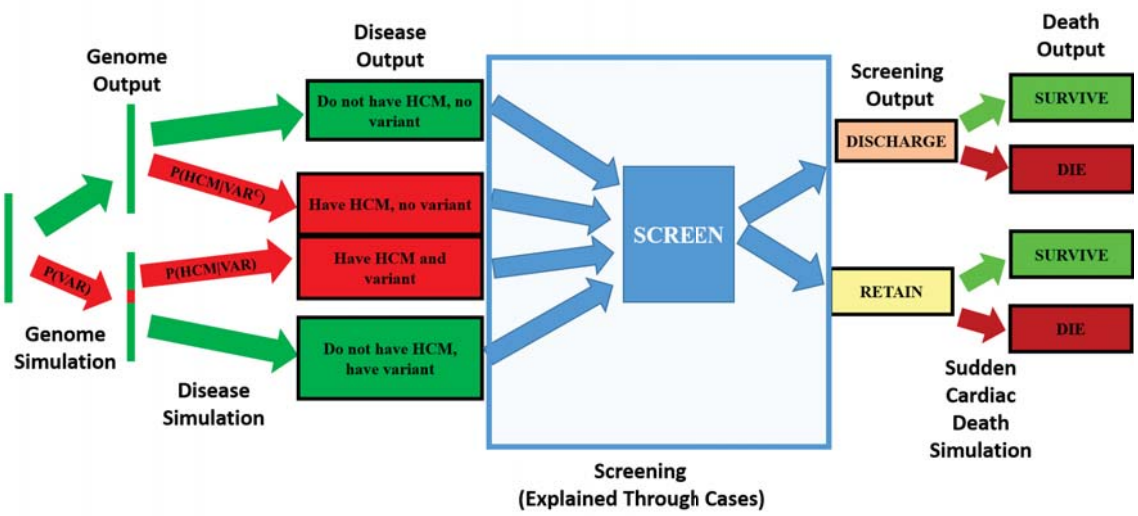


Figure I-1: Overview of cost/benefit simulation

many variants we chose from the ranked variant list to include as "pathogenic." We varied this number from 90 variants (only ClinVar variants) to 400 variants (310 additional variants from model).

2. **Simulate HCM in population:** In order to simulate HCM, we had to find $P(HCM|VAR)$ and $P(HCM|VAR^C)$. These values were not precise in the literature, and so we found them indirectly through Bayes' Theroem as illustrated in Equations I-1 and I-2. To determine these probabilities, $P(HCM) = 0.002$ [3], $P(VAR)$ was found from step 1 above using the gnomAD database, and $P(VAR|HCM)$ was varied from 0.5 to 0.9, which we found to be an acceptable range from the literature [5, 3].

$$P(HCM|VAR) = \frac{P(HCM)P(VAR|HCM)}{P(VAR)} \tag{I-1}$$

$$P(HCM|VAR^C) = \frac{[1 - P(VAR|HCM)]P(HCM)}{1 - P(VAR)} \tag{I-2}$$

3. **Simulate Screening Cases:** We simulated six different screening cases, described in Table I-3. A max-accuracy echocardiogram was simulated to have a sensitivity of 0.851 and specificity of 0.851. A max-specificity echocardiogram was simulated to have a sensitivity of 0.607 and specificity of 0.999. Genetic testing was simulated at 100% accuracy.

4. **Simulate Sudden Cardiac Death:** Sudden cardiac death was determined by $P(SCD|HCM) = 0.0081$ per year [6]. Two separate simulations were run: one for officers, another for enlisted. Officers spend an average of 11 years in the military, and enlisted spend an average of 7 years in the military [7].

Table I-3: Cases Being Compared in Cost/Benefit Analysis

Case 1	No screening for HCM implemented
Case 2	Echocardiogram screening only, maximum accuracy settings
Case 3	Genetic screening followed by echocardiogram screening for positive genetic test, maximum accuracy settings
Case 4	Echocardiogram screening only, maximum specificity settings
Case 5	Genetic screening followed by echocardiogram screening for positive genetic test, maximum specificity settings
Case 6	Genetic screening only

The simulations were run 1000 times for each combination of the number of ranked variants we included from the ranked variant list ($\#\ of\ variants$; from 90-400) and the $P(VAR|HCM)$ (from 0.5-0.9). In this report, we display averages over the 1000 simulations.

2.2.3 Survey

We created a 21-question survey to assess individuals' attitudes regarding genetic screening in the military. The survey was approved by the United States Naval Academy HRPP and was distributed to all military personnel at USNA via email.

2.3 Results

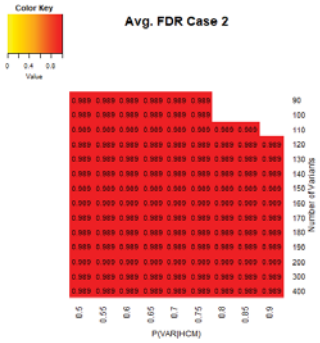
2.3.1 Cost/Benefit Analysis

We display in this synopsis three measures for measuring the effectiveness of each of the six screening cases.

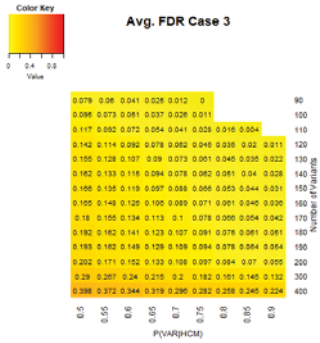
Firstly, we display the False Discovery Rate (FDR), defined by equation I-3. The FDR is a measure of the number of false positives in a test: the higher FDR, the more false positives. The average FDR among the 1000 officer simulations for each combination of $\#\ of\ variants$ and $P(VAR|HCM)$ is displayed in Figure I-2. Enlisted simulations had similar values for FDR.

$$FDR = \frac{\#\ of\ individuals\ discharged\ and\ NOT\ diseased}{\#\ of\ individuals\ discharged} \tag{I-3}$$

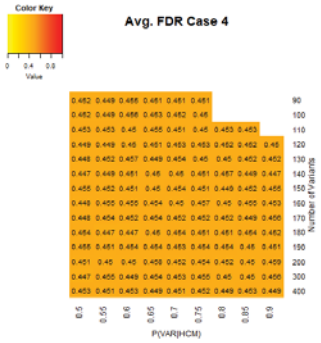
Notice how, in Figure I-2, the FDR is highest for Case 2 and is constant (around 0.99), and the FDR is still relatively high and constant for Case 4 (around 0.45). FDR varies for different values of $\#\ of\ variants$ and $P(VAR|HCM)$ for Cases 3, 5 and 6, with a lower FDR corresponding to lower $\#\ of\ variants$ and higher $P(VAR|HCM)$.



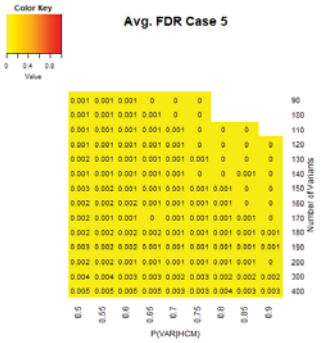
(a) Case 2
σ: {0.002, 0.002, 0.002, 0.002, 0.002}



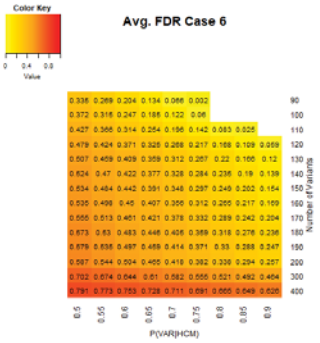
(b) Case 3
σ: {0.003, 0.005, 0.006, 0.008, 0.1}



(c) Case 4
σ: {0.08, 0.08, 0.08, 0.08, 0.09 }



(d) Case 5
σ: {0, 0.006, 0.009, 0.012, 0.026}



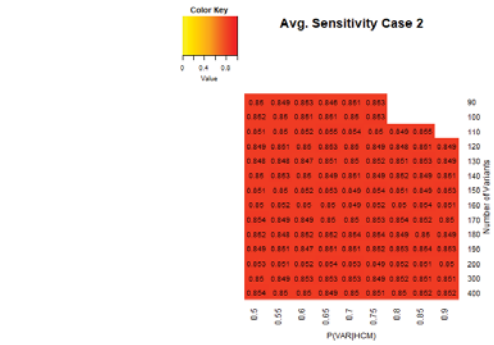
(e) Case 6
σ: {0.009, 0.067, 0.077, 0.083, 0.098}

Figure I-2: Heatmaps of the average FDR for each Officer case.
Standard deviation summary given as: σ: {min, 25th quantile, median, 75th quantile, maximum}.

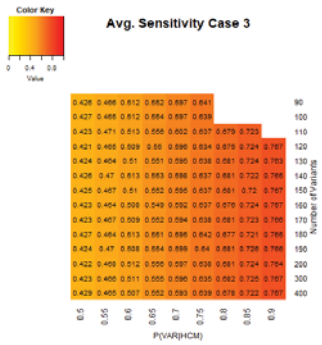
Next, we display the sensitivity, or true positive rate (TPR) of the Cases. The sensitivity is defined according to Equation I-4. A higher sensitivity means that more individuals with HCM are identified by the screening test, thus increasing true positives and decreasing false negatives. Figure I-3 displays the sensitivity of each officer Case over the 1000 officer simulations for each $\#\ of\ variants$ and $P(VAR|HCM)$ combination. Enlisted values were similar to the officer values.

$$Sensitivity = \frac{\#\ of\ people\ discharged\ and\ diseased}{\#\ of\ people\ diseased} \tag{I-4}$$

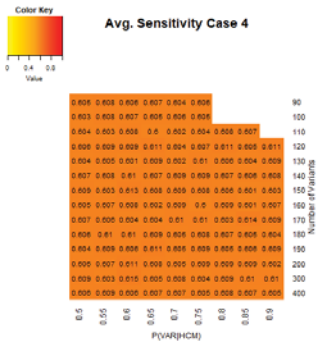
Note how the sensitivity for Cases 2 and 4 appears not to change, and the sensitivity for Cases 3, 5 and 6 changes with different values of $\#\ of\ variants$ and $P(VAR|HCM)$. The sensitivity ranges from approximately 0.4 to 0.75 for Case 3, 0.3 to 0.55 for Case 5, and 0.5 to 0.9 for Case 6.



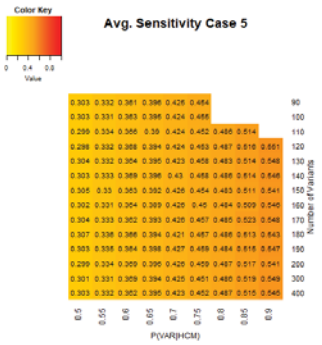
(a) Case 2
σ : $\{2.05, 2.21, 2.24, 2.27, 2.36\}$



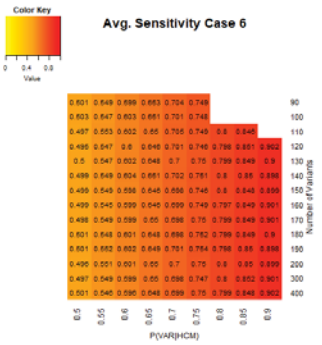
(b) Case 3
σ : $\{2.70, 3.26, 3.74, 4.13, 4.49\}$



(c) Case 4
σ : $\{3.41, 3.54, 3.60, 3.65, 3.77\}$



(d) Case 5
σ : $\{3.78, 4.16, 4.40, 4.63, 5.02\}$

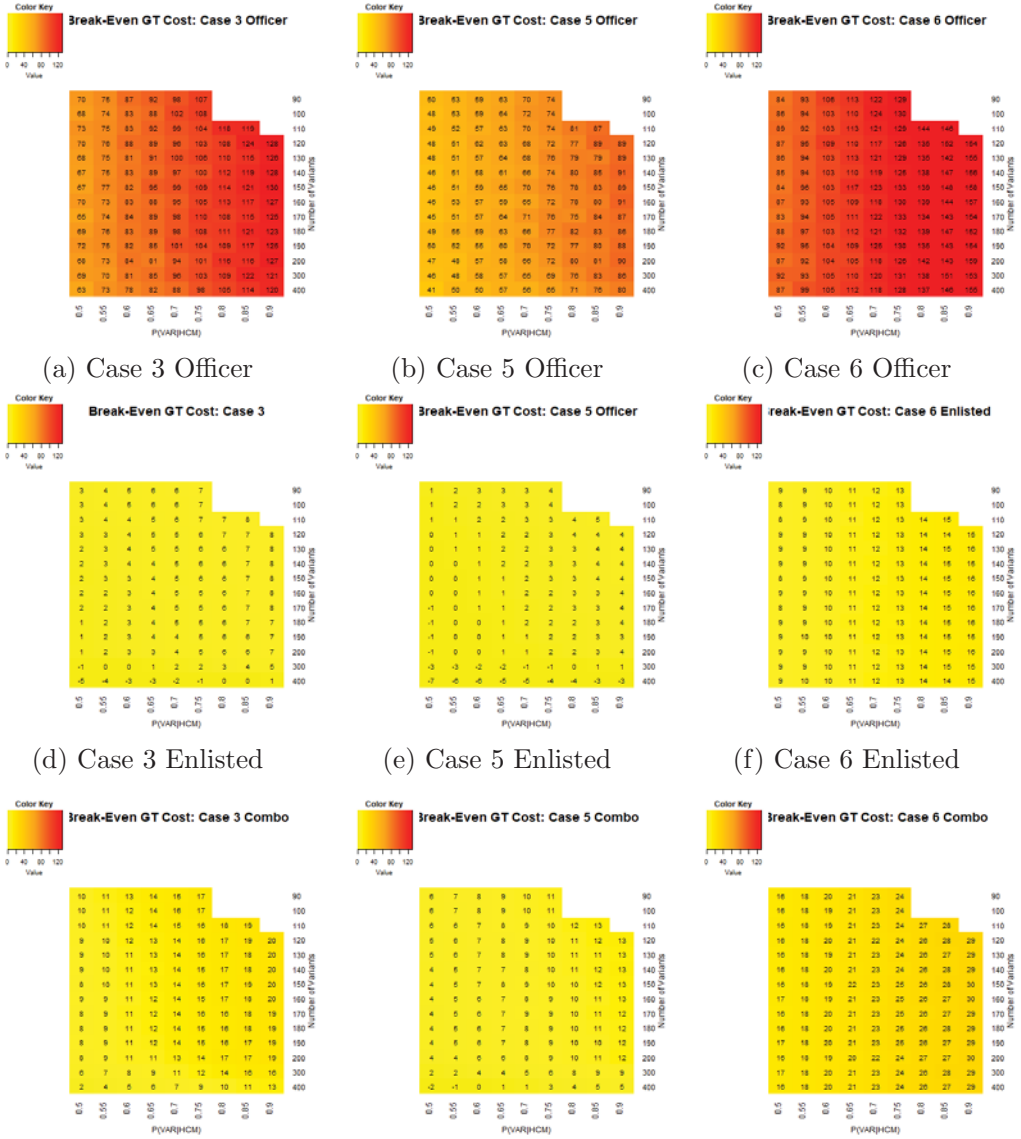


(e) Case 6
σ : $\{1.76, 2.60, 3.25, 3.71, 4.19\}$

Figure I-3: Heatmaps of the sensitivity for each officer case. Standard deviation summary given as $\sigma : \{min,\ 25^{th}\ quantile,\ median,\ 75^{th}\ quantile,\ maximum\}$

Finally, we display the "break even genetic test cost." We calculated the cost of each screening case by comparing the cost of doing nothing (Case 1) to the cost of the screening cases (Cases 2-6). The costs were arrived at by taking into account the cost of screening, and the cost incurred by the military when someone dies due to gratuity costs and forfeited training costs. Cases 2 and 4 (an echocardiogram on the entire population) were prohibitively expensive. The "break even genetic test cost" is the cost at which a genetic test must fall to for Cases 3, 5 and 6 at which the military will start to see a monetary benefit.

We display these break-even genetic test (GT) costs in Figure I-4. It can be seen that the break-even GT costs for the officer-only simulation range from approximately \$50 to \$130. For the enlisted-only simulation, break-even GT costs range from below \$0 to approximately \$20, and for the officer and enlisted combination, the costs range from below \$0 to approximately \$30. The reason for the lower break-even GT costs associated with the enlisted populations is due to the lower training costs of enlisted personnel as well as the shorter time enlisted personnel spend in the military on average.



(a) Case 3 Officer (b) Case 5 Officer (c) Case 6 Officer

(d) Case 3 Enlisted (e) Case 5 Enlisted (f) Case 6 Enlisted

(g) Case 3 Combined (h) Case 5 Combined (i) Case 6 Combined

Figure I-4: Heatmaps of the average value for cost of a genetic test when Net benefit = 0 for an officer only (top), enlisted only (middle), and combined officer and enlisted simulation (bottom).

2.3.2 Survey Results

We found from our survey that approximately 70% of individuals are curious about their disposition to develop genetic disease, and an overwhelming majority ($> 90\%$) would want to know if they had a genetic condition that was treatable. However, approximately 60% of individuals list either losing their job or insurance as their #1 concern regarding genetic screening. Only around 15% of individuals agree that genetic screening should be implemented to make employment decisions in the military. Confidentiality is also a concern, with around 60% of individuals agreeing it would be a concern for them if genetic testing were implemented. Individuals who had spent more time in the military were more likely to be opposed to genetic testing. Despite this, almost 50% of individuals agreed an individual should be prevented from piloting aircraft given a scenario in which a genetic test showed they had substantial risk of sudden cardiac death.

2.4 Discussion and Conclusion

We found the FDR of Cases 2 and 4, as well as the cost, to be too prohibitively high to be considered effective for population-level screening. The FDR for Case 6 is prohibitively high for some combinations of $\#\ of\ variants$ and $P(VAR|HCM)$. The FDR of Cases 3 and 5 was found to be adequate, however. We also found the break even genetic test cost to be roughly \$50 to \$130 for Cases 3, 5, and 6 for an officer-only simulation and below \$0 to \$30 for a combined officer and enlisted simulation. Based on the current cost of genetic tests, we speculate that a DNA microarry is or may in the near future be monetarily feasible to achieve the break-even cost in the officer population, and even possibly the officer and enlisted combined population. We conclude that Cases 3 and 5 are the best overall screening Cases to implement, with Case 5 having less false positives but a lower monetary benefit than Case 3.

From the survey, we conclude that individuals in the military are overall not inherently opposed to genetic testing and do desire to use it to determine diseases they may posses. However, many individuals in the military are concerned about and opposed to implementation of genetic screening in the military to make employment decisions, and are also concerned about its confidentiality.

Overall, we conclude that genetic screening in the military to detect Hypertrophic Cardiomyopathy may be feasible from a specificity and cost/benefit standpoint if a microarray is used and it is followed-up with an echocardiogram. However, the military will need to address ideological barriers to the implementation of genetic screening in order for it to be effective. We also note that genetic screening has the potential to detect more than one condition (possibly keeping costs constant and increasing benefit), and also has the potential to become more accurate as population-level screening is implemented.

Contents

List of Figures

List of Tables

3 A Primer on Screening Tests and Statistics

The concepts of statistics relating to screening tests permeate this entire report. Some concepts of statistical analysis will be explained in the content of the report while data are being presented, however a basic understanding of statistics and screening tests will be useful before beginning to read the report.

Medical screening tests look to identify individuals who have a disease, while not identifying individuals who do not have disease. This twofold goal is quantified by maximizing true positives and true negatives, and minimizing false positives and false negatives. Figure 1 indicates the definitions of false positives, false negatives, true positives, and true negatives.

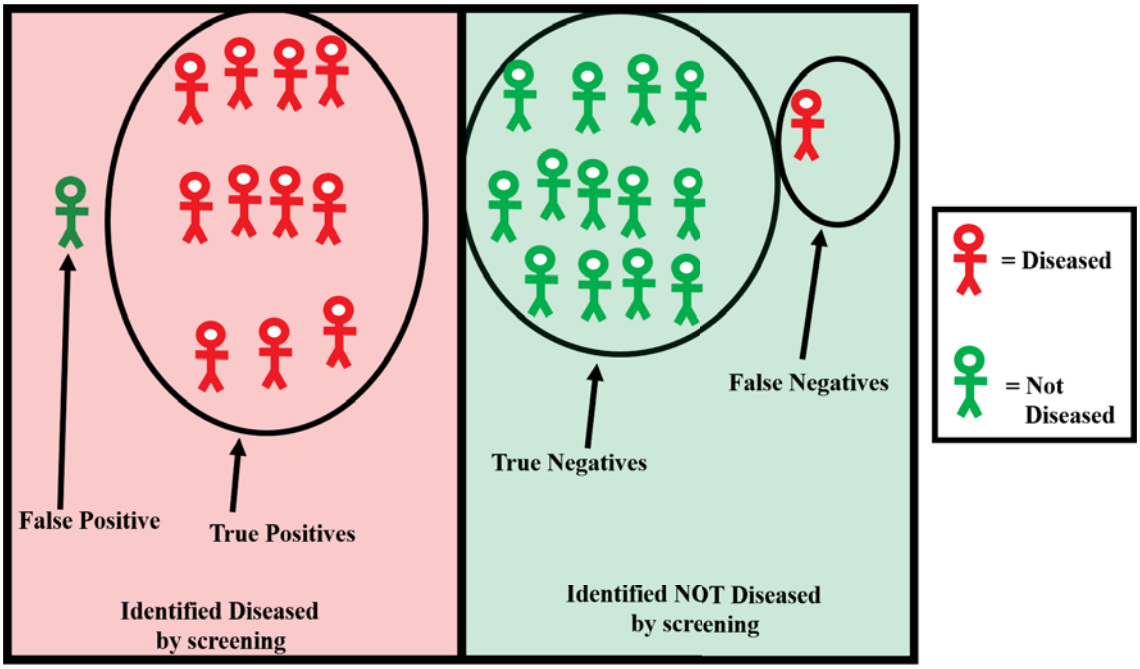


Figure 1: In a disease screening test, false positives are individuals that do not have the disease but are identified as having it, and false negatives are individuals that have the disease but are not identified as having it. These concepts may be applied to any binary condition test.

Optimally, a screening test will minimize the number of individuals it incorrectly identifies. However, often, changing the value for one factor will cause other factors to change as well. Some screening tests may desire to be more selective, and will tolerate missing individuals (false negatives), but will want to make sure that individuals identified by the test truly have the condition (minimize false positives). On the other hand, some tests can tolerate misidentifying individuals as positives, but will not tolerate individuals being classified as erroneously negative.

4 Motivation

At a molecular and structural level, there is a good understanding of what makes up our genetic code: the deoxyribonucleic bases adenine, thymine, cytosine, and guanine. In 2003, the successful completion of the human genome project ushered in an era of optimism that humans could understand the letters of the genetic code that caused common and uncommon diseases. However, since then, it has been evident that the human genome affects development and pathogenesis in ways that are too complex for humans, and even the most sophisticated computer algorithms, to completely understand at the present moment [1].

Despite this undeniable complexity, understanding of the human genome has progressed significantly over the past decade and the ability to sequence the human genome has been brought to nearly all individuals. Although the sequencing of the first human genome took decades and over a billion dollars, a genome can be accurately sequenced today in less than a day for less than $1,000 through next generation sequencing techniques. Online databases that are accessible to everyone have specific genetic variations listed that are known to cause disease. New disease-causing "pathogenic" mutations are being discovered every day, and advanced computer algorithms are being used to develop genetic models for complex multigenic diseases. Medical genetics has become a distinct medical specialty, and knowledge of genetics has grown to encompass nearly every medical specialty in existence [13].

One of the most important pieces of information that the genome can give is a person's disposition for certain diseases. The goal of genetic screening is to survey the genome looking for variants: deviations from the regular sequence of DNA base pairs A, C, G, and T; that cause disease. By identifying these "pathogenic variants" in an individual's genome, the individual may be made more aware of their likelihood of developing disease. Screening for certain genetic conditions may reduce significantly the morbidity, mortality, and impact on the quality of life of individual affected by these diseases [14].

Although the prospect of genetic screening is large, many setbacks also exist in its implementation. Due to our primitive understanding of complex genetics, the mere existence of a pathogenic variant does not always indicate the presence or eventual development of disease. This is because most genetic conditions depend on not one but many different genes that interact with each other and the environment to produce a phenotype, or physical manifestation [14]. However, for many genetic conditions, there are certain variants that greatly increase the chance for an individual to develop a specific disease.

It is then necessary, before genetic screening be implemented in any population, to assess the degree to which a population may benefit from this screening. A concern with the viability of genetic screening, and any diagnostic test, is assessing the amount of false negatives and false positives produced from the test when implemented in the population. A test that will return false negatives will be ineffective in diagnosing conditions, and a test that will return false positives may place more burden on the patient and healthcare system than necessary. Additionally, medical tests cost money and may or may not make monetary sense to implement. Tests may also have a psychological impact on individuals, and opinions on medical testing may impact the population of the individuals that

undergo the testing. The goal of this study will be to determine if implementation of genetic screening in the military (a population of seemingly healthy individuals) may help identify individuals who have life-impacting genetic conditions without prohibitively costing the military money, or cause discontent due to the opposition and the psychological impact of the tests in the force.

4.1 Applicability to Military

Due to the physical nature of military work, genetic screening is of even greater importance in the military. Kruszka et al. emphasized the use for genetic screening to uncover long QT syndrome, which is a cause of sudden cardiac death (SCD) [14].

The impact of sudden cardiac death on the military is not insubstantial. Eckart et al. studied autopsy reports over a 25 year period from military recruit training (1977-2001). 277 non-traumatic deaths were identified during recruit training, of which 148 autopsy reports were available. Of these 148, around half were sudden cardiac deaths [15]. Diseases such as hypertrophic cardiomyopathy (HCM), long QT syndrme, and myocardidis were the main causes of SCD. The military is an especially important area for the identification of sudden cardiac death due to the strenuous physical demands placed on its members, as over 90% of SCD in the young is manifested during exercise. Another study performed by Eckart et al. analyzed 1,044 sudden cardiac deaths throughout the entire Department of Defense over the course of 10 years. Many of these deaths were due to a genetic cause, such as HCM or long QT syndrome that could have been prevented through the use of genetic screening [2].

The military may use genetic screening to prevent sudden cardiac death as Kruszka et. al. states, but also may use genetic screening for a number of other important conditions. Aggressive cancers, or predisposition to aortic aneurysms are other diseases that may be investigated with genetic screening and have special importance in the military.

Currently, the military uses genetic screening to identify individuals with sickle cell trait (SCT) and Glucose 6-phosphate dehydrogenase (G6PD) deficiency. Although these tests are for genetic conditions, they are not true genetic tests: they test for the phenotypic effects of genetic disease (the absence of normal hemoglobin for SCT and deficiency of the G6PD enzyme in cells) instead of investigation of the genomes themselves [16].

4.2 Ethical Implications of Study

It must be noted, however, that the ethical implications of genetic screening are far reaching and very significant. Genetic screening has implications in employment and health insurance, as employers and insurers could, with the advancement of genotype-phenotype correlations, discriminate based on genetic results or conditions. Current law prevents this discrimination for all non-government employers.

The Genetic Information Nondiscrimination Act of 2008 (https://www.eeoc.gov /laws/statutes/gina.cfm) prohibits employers from refusing to hire or discriminate against any employee, and prevents insurers from making decisions about eligibility for insurance, insurance cost or insurance coverage based on results of genetic information. In addition, it prohibits

employers or insurers from forcing employees or clients to undergo genetic testing, unless such genetic testing is to monitor the health of an employee due to dangerous work environments required by law. Therefore, genetic screening could not lawfully be used by any civilian employer or labor union for the purpose of excluding individuals from employment, or be used by insurance companies to alter coverage or insurance rates.

The military, unlike any civilian employer, allows selection of individuals based on genetic results [16]. However, as genetic screening advances, the question of how genetic results will be used by the military to assess the fitness of an individual for duty will become more important. Some genetic conditions are disqualifying in the military, including sickle cell anemia, long QT syndrome, and hypertrophic cardiomyopathy. The military, however, does not use genetics to test for these conditions, and instead only monitors the phenotypic effects of the disease. The question must be eventually approached whether the military should begin using genetics to identify individuals with these conditions.

Additionally, the impact of genetic screening will also be relative to the number of false positives and false negatives that it returns. If too many false positives are recorded for a specific condition, the burden on the healthcare system and individuals would be significant. Individuals who have positive genetic tests likely will suffer anxiety associated with that positive result. In addition, if many expensive and timely procedures are undertaken in order to confirm the genetic tests, it will impose a heavy burden on the healthcare system that may cause healthcare costs to increase significantly. A large number of false negatives would make a genetic test virtually useless, as it will allow for individuals that possess disease to be undetected by the test.

5 Overview of Project Method

This project looks to assess the viability of genetic screening by determining the overall cost or benefit genetic screening may offer the military, as well as assessing the current attitudes of genetic screening in the military. There are three main phases to this project:

1. **Perform a genetic analysis to find pathogenic variants in an asymptomatic population.** We looked through the gnomAD database to find genomic variants that may predict disease. First, the ClinVar database was analyzed for pathogenic variants part of the American College of Medical Genetics list of Recommendations for Reporting of Incidental Findings [17]. The frequencies of these variants in the gnomAD database were used to draw conclusions about how the screening for these conditions may impact individuals in the military. Secondly, the ClinVar database along with several genetic parameters were used to develop a logistic regression model that predicted the pathogenicity of variants for hypertrophic cardiomyopathy in the gnomAD database. The results from this analysis were used to perform a cost benefit analysis listed in phase 2 below.

2. **Perform a cost/benefit analysis of genetic screening in the military.** A cost-benefit analysis of performing genetic screening for hypertrophic cardiomyopathy on a military population was performed. This produced a monetary value of cost and benefit that genetic screening will likely produce if implemented, as well as give an estimation on the number of false positives and false negatives that may

result from the tests. The results from this analysis may be used to determine how genetic screening may be implemented currently or in the future, and may serve as a model for determining the benefit of screening other large, asymptomatic populations.

3. **Perform an analysis of the current attitudes of genetic screening in the military** A survey was created and distributed to all military members at the United States Naval Academy. The results from this survey gauge how the force will receive a genetic test, and if education in genetics may make individuals more or less open to the idea of genetic screening. The survey also assesses how individuals feel about receiving a genetic result that may impact their career.

6 Finding Pathogenic Variants in an Asymptomatic Population

In order to perform genetic screening, pathogenic variants must be located in the genome. A pathogenic variant is a genetic variant that causes disease.

6.1 Overview of Genetic Variation

Genetic screening will ultimately look at an individual's genome and determine whether an individual has susceptibility to genetic disease based on the base pairs in their genome. A genome is comprised of 23 chromosome pairs which contain over 3 billion nucleotide base pairs: the A, C, G, and T that make up the genetic code. DNA is a double-stranded molecule, and Adenine (A) will prefer to pair up with Tyrosine (T), while Cytosine (C) will prefer to pair up with Guanine (G). This study will focus on single nucleotide polymorphisms (SNPs; see Figure 2) which occur when a single nucleotide base pair changes to another base pair (eg. A G-G pair changes to a T-A pair).

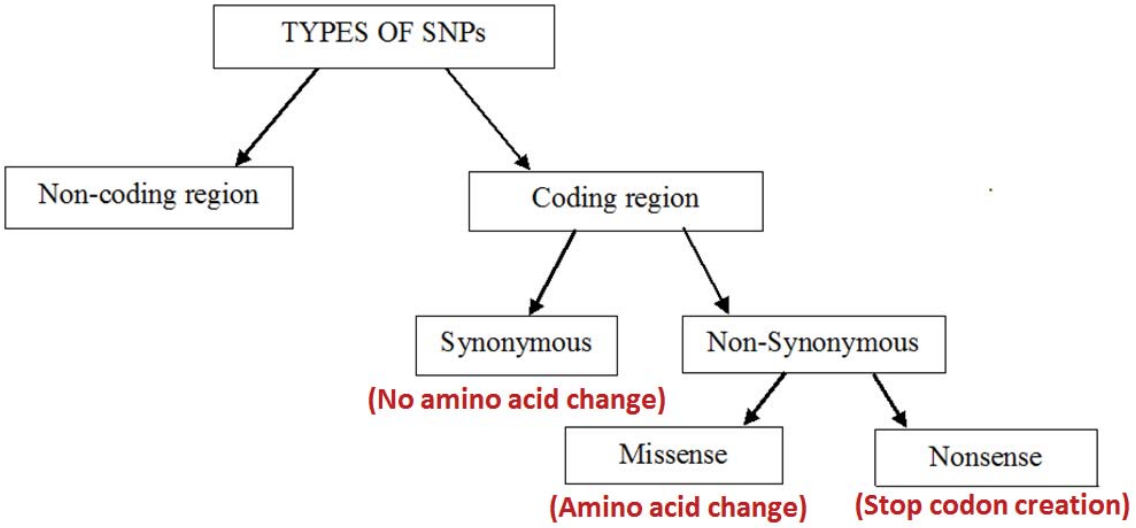


Figure 2: Single Nucleotide Polymorphisms [18].

This study will also look to detect pathogenic insertions and deletions (INDELs; see Figure 3). INDELS occur when extra genetic information is inserted in the genetic code (insertion) or when genetic information is removed from the genetic code (deletion). INDELs may cause frameshift mutations, which is when the "reading frame" of the DNA sequence is changed, altering protein structure significantly.

In order to understand genetic pathogenicity in general, it is important to understand how DNA serves as the blueprint for the processes of nearly all life. The primary structural components of life that cause organisms to do things are proteins. Proteins are polymers of many amino acids, which are molecules containing amine and carboxyl functional groups along with a side chain. The differing properties of the side chains of the

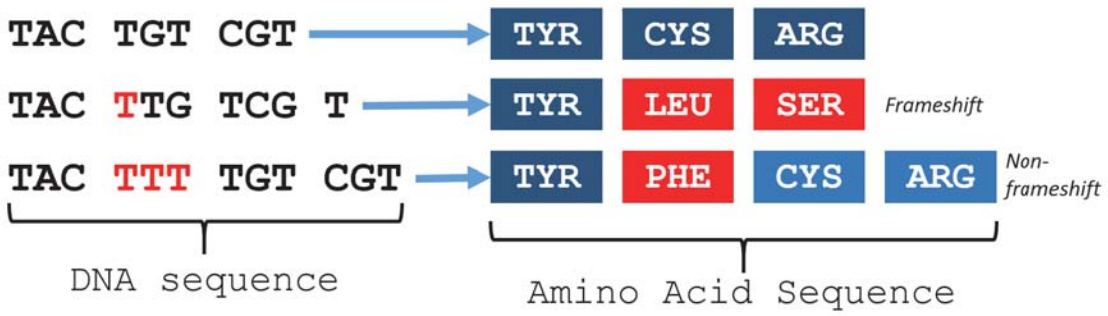


Figure 3: Genetic Insertions. Deletions will follow the same pattern, with DNA sequence deleted instead of inserted into the genome. A frameshift INDEL will occur if nucleotides are inserted or deleted in multiples other than three.

amino acids is what allows proteins to take very complex and diverse shapes. Many different factors cause proteins to fold into the complex structures that are required to perform functions in life, but one of the most important factors in protein structure and function is the unique sequence of amino acids that make up a protein. If a protein's amino acid sequence changes, it is possible that it could fail to perform the function required of it, or perform a detrimental function to the organism.

The central dogma of molecular biology, as illustrated in Figure 4, states that DNA codes for RNA, which ultimately codes for the amino acid sequence that makes up proteins. By changing the sequence of coding DNA, the sequence of RNA is changed, which may also change the amino acid sequence in proteins. However, it is important to note that not every DNA change will necessarily change the amino acid sequence both because there are several DNA sequences that code for the same amino acid (these are known as synonymous mutations in Figure 2), and because not all genetic information actually codes for proteins [3].

The exome is the protein coding region of the genome, and makes up for only 2% of the entire human genetic code. The rest of the human genetic code is made up of various non-coding regions that may serve as regulatory sites, sites that tell other portions of the genome what to do, or may simply be "evolutionary baggage." Most of the human disease discovered today is within the exome, and most genetic disease studies focus only on interpreting genetic information from the exome [19]. This study will focus on the SNPs and INDELs that are part of the exome, however may consider regions that are noncoding if sufficient evidence has been gathered that proves the region's pathogenicity.

6.2 Determining a Population

A genetic population that is similar to the military's must be found to properly simulate the effect genetic screening may have on the military. This population must be comprised of individuals that are asymptomatic for overt genetic conditions and would pass an entrance-level military physical exam. However, although these individuals may be overtly healthy, it is still possible for them to harbor genetic disease such as conditions that cause sudden cardiac death, aggressive cancers, or aortic aneurisms.

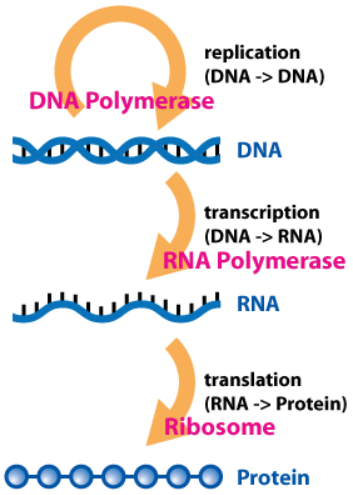


Figure 4: The Central Dogma of Molecular Biology is important to understand how changes in genetic code can cause genetic disease [20].

The gnomAD database is a genetic database that includes genetic information from individuals of all ethnicities from over 20 independent genomic research studies, and has "removed individuals known to be affected by severe pediatric disease, as well as their first-degree relatives" [21]. Because of this, the gnomAD database provides a population of more than 120,000 individuals that are overtly healthy. However, the gnomAD database does not remove individuals that may harbor other unknown genetic conditions. Therefore, this population is a very good representation of the military population.

It is important to note that the gnomAD database provides de-identified and fragmented genomes. This means that gnomAD, for purposes of privacy, does not associate whole genomes or exomes together. Instead, gnomAD simply counts the number of alleles at each genetic locus, and provides information for how many variant alleles there are at a locus. An illustration of this is shown in Figure 5.

The gnomAD database provides a useful overtly healthy population, and its information can be used to identify how many individuals in this overtly healthy population possess variants that cause genetic disease.

It is important to note that variants found in the gnomAD database in this study are assumed to be at their natural frequency in the general population. The gnomAD database contains 123,136 exomes and 15,496 genomes as of November 2017, and rare variants are presumed to have the same frequency in gnomAD as they would in any healthy population gathered [21]. Although this assumption is the best one that can be made with a relatively large population, it is possible that rare variants may be under or over-represented in this limited population compared to the overall general healthy population.

6.3 Pathogenic Variants in ClinVar

Finding an adequate population of individuals for analysis is only the first step of the process. Next, certain variants in the population must be identified as pathogenic.

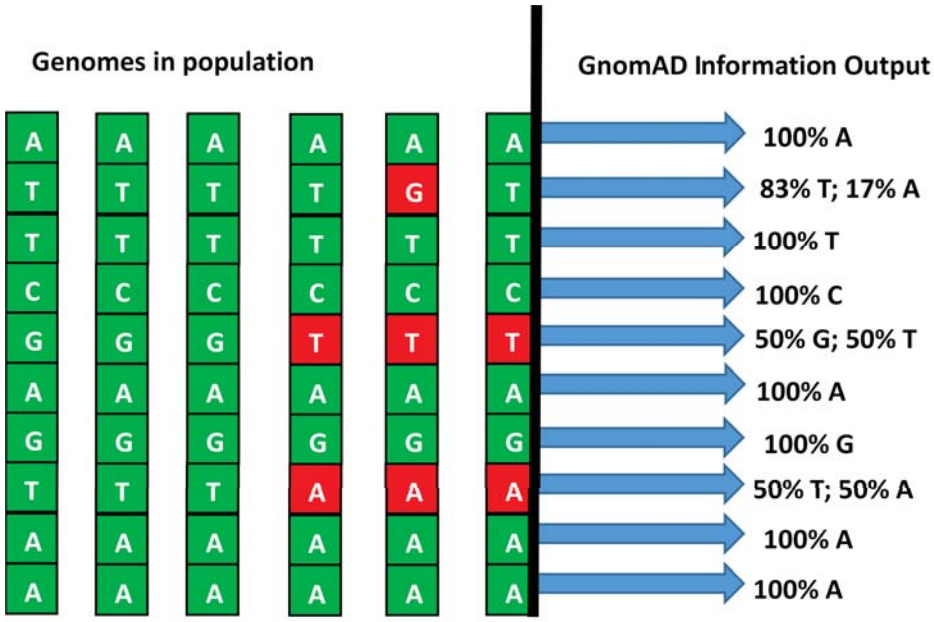


Figure 5: The gnomAD database does not associate whole genomes together. Instead, it reports how common alleles are in the population.

ClinVar is a database that classifies variants as disease causing or not disease causing based off of scientific studies that suggest or prove that a certain variant is disease causing or benign. This database may be used directly to identify pathogenic or benign variants in the population [22].

Originally, pathogenic variants were to be determined in this study based solely on their classification in the ClinVar database. A computer program was written that determines the frequency of pathogenic variants in any gene in the gnomAD database according to its classification in ClinVar. The frequency of ClinVar pathogenic variants in the gnomAD database for the 29 genes that have diseases applicable to the military is shown in Table 1. These genes were chosen based on their relevance to disease and severity classification by the American College of Medical Genetics [17], as well as the diseases they cause being applicable to adult individuals that undergo high-strenuous activity. However, the data presented in ClinVar is neither complete nor wholly accurate.

ClinVar uses the American College of Medical Genetics (ACMG) classification of variants from their "Standards and Guidelines for the Interpretation of Sequence Variants" [17] These guidelines give five potential categories for variants of investigation: Benign, Likely Benign, Uncertain Significance, Likely Pathogenic, and Pathogenic. There are complicated standards that go along with each classification, but the general consensus is that benign and pathogenic variants are to be 99% certain of being benign (not disease causing) or pathogenic (disease causing) respectively. Likely benign/pathogenic variants are to have 90% certainty of their clinical significance. The remainder of variants are placed under the category of "variants of uncertain significance." These assertions may be found in various ways, from direct clinical observation of pathogenicity to model organism stud-

Table 1: List of Frequency in gnomAD database of ClinVar Pathogenic Variants for Conditions Most Applicable to the Military

Gene	Disease	Frequency in gnomAD
ACTA2	Aortic Aneurism	9.69 E-5
BRCA1	Hereditary Breast/Ovarian Cancer	7.34 E-4
BRCA2	Hereditary Breast/Ovarian Cancer	1.52 E-3
COL3A1	EDS- vascular type	4.05 E-5
DSC2	right ventricular cardiomyopathy	9.55 E-5
DSP	right ventricular cardiomyopathy	1.88 E-3
PKP2	right ventricular cardiomyopathy	2.53 E-4
TMEM43	right ventricular cardiomyopathy	1.50 E-4
DSG2	right ventricular cardiomyopathy	1.29 E-3
FBN1	Aortic Aneurisms	5.42 E-4
TGFBR1	Aortic Aneurisms	9.66 E-5
TGBBR2	Aortic Aneurisms	1.10 E-3
SMAD3	Aortic Aneurisms	1.23 E-5
ACTA2	Aortic Aneurisms	9.69 E-5
MYLK	Aortic Aneurisms	4.07 E-6
MYH11	Aortic Aneurisms	2.34 E-4
MEN1	Multiple Endocrine Neoplasia Type 1	8.13 E-6
MLH1	Lynch Syndrome	2.33 E-1
MSH2	Lynch Syndrome	1.16 E-2
MSH6	Lynch Syndrome	5.15 E-3
PMS2	Lynch Syndrome	5.35 E-3
MUTYH	MYH-Associated Polyposis	5.64 E-3
MYH7	Hypertrophic Cardiomyopathy	5.55 E-4
MYBPC3	Hypertrophic Cardiomyopathy	9.47 E-4
NF2	Neurofibromatosis type 2	4.06 E-6
SDHD	Hereditary Paraganglioma-Phenochromocytoma Syndrome	1.38 E-2
SDHAF2	Hereditary Paraganglioma-Phenochromocytoma Syndrome	2.03 E-5
SDHC	Hereditary Paraganglioma-Phenochromocytoma Syndrome	8.55 E-5
SDHB	Hereditary Paraganglioma-Phenochromocytoma Syndrome	1.63 E-2

ies of variants to computer simulations [22]. The ClinVar database may be modified by anyone in the scientific and medical communities, and provides references to supporting evidence for genetic variant assertions. ClinVar, because of the ability for anyone in the scientific or medical community to classify variants, may have incorrect variants of classification. Therefore, it is important to carefully examine each variant classification in ClinVar to assure that it is categorized with consistent support from empirical evidence. If studies debate the significance of a variant, then it should not be classified as a known pathogenic variant.

From Table 1, it can be seen that some conditions have a low frequency of pathogenic variants, and some conditions have a higher frequency of pathogenic variants (such as MLH1). If all of the frequencies of pathogenic variants for these 29 genes were added, it would total a frequency of 0.305. This means that, if the variants are inherited indepen-

dently and each individual only has one variant, approximately 30% of the population would have a pathogenic variant. However, rare genetic disease does not occur in 30% of the population. This situation illustrates two things: that having a pathogenic variant does not necessarily mean that an individual will have disease, and some pathogenic variants may be misclassified.

ClinVar is also incomplete. The diseases that are being studied in this project occur in low frequencies in the population. Diseases may be caused by hundreds of different mutations in a single gene, and therefore many of the variants that exist in a general population that cause disease will not have been previously examined in ClinVar due to their rarity. Because of this, it is important to realize that the number of pathogenic variants found in ClinVar likely does not include all of the pathogenic variants in the total population of individuals.

The question of how to uncover these undiscovered pathogenic variants as well as assure that the variants used from ClinVar are accurate must be answered before progressing father. To do this, logistic regression models were built around the two genes that most commonly cause the disease hypertrophic cardiomyopathy.

7 Building A Model For Predicting Pathogenicity in Hypertrophic Cardiomyopathy

7.1 Logistic Regression Model

To uncover undiscovered pathogenic variants, a logistic regression model was developed that best predicted the pathogenicity of variants in ClinVar. The logistic regression model is built upon Equation 1.

$$p = \frac{e^{\alpha+\beta_n X}}{1 + e^{\alpha+\beta_n X}} \tag{1}$$

Logistic Regression is used to identify the percentage probability of a binary result occurring (a binary result is a "yes/no" result: there are two possibilities). The parameters in the logistic regression model are represented as X in the equation. β represents a coefficient that is given to each parameter to fit it to a curve. Multiple parameters may be used in the equation as multiple X and β terms. p is the output of the model, and is the probability that a result will occur based on the values of the parameters. α is the intercept of the equation that is used to normalize the equation.

In this case, logistic regression was used to identify the probability that a certain variant is pathogenic. ClinVar data was used to train the model. Variants from ClinVar were assumed to be correct: a variant classified as "pathogenic" or "likely pathogenic" with no conflicting interpretations was assumed to be pathogenic, and a variant classified as "benign" or "likely benign" with no conflicting interpretations was assumed to be benign. Each variant had several parameters associated with it, discussed in Section 7.5. These parameters were used to guide the model to make predictions of pathogenicity. Figure 6 is an example of a logistic regression model. This model was generated by matching parameters with a pathogenic/benign result using the software R [23]. The green dots represent known pathogenic variants (at 1.0 probability) and known benign variants (at 0.0 probability). The parameter(s) used to guide the model are based off of these green dots, and the red line is the model result. Figure 5 indicates that at around a parameter value greater than 30, approximately 100% chance of pathogenicity occurs, and at a parameter value less than 10, approximately 0% chance of pathogenicity occurs. Between 10 and 30, variable probabilities of pathogenicity occur.

Using a logistic regression model, an arbitrary cutoff of what makes a variant pathogenic can be used. This means that, if a cutoff is set at 90%, all variants the model assigns with a greater than 90% chance of being pathogenic are the only variants classified as pathogenic according to the model. If a cutoff of 60% is used, variants with a greater than 60% chance of being pathogenic according to the model are classified as pathogenic. This ability to adjust the cutoff allows for greater flexibility in determining pathogenic variants.

7.2 Hypertrophic Cardiomyopathy, MYBPC3 and MYH7

The logistic regression model will be trained using ClinVar data from two genes, MYH7 and MYBPC3, which are known to cause Hypertrophic Cardiomyopathy. The high frequency and relevance of hypertrophic cardiomyopathy to the military, in addition to its

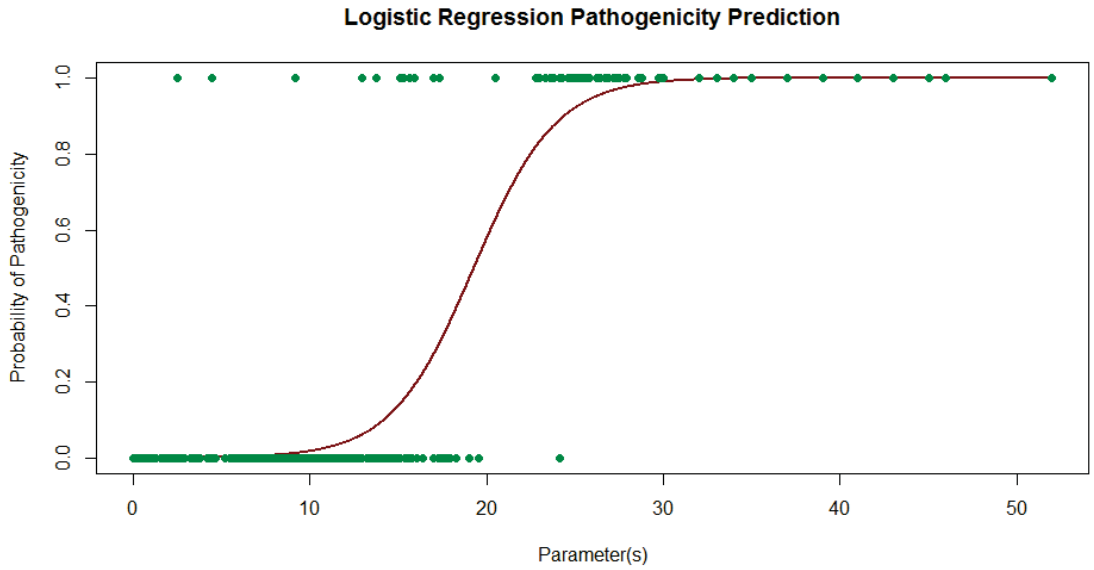


Figure 6: Example Logistic regression model predicting the pathogenicity of variants based on certain parameters.

genetic causes, make it a good condition on which to base the model and the rest of the cost/benefit simulations.

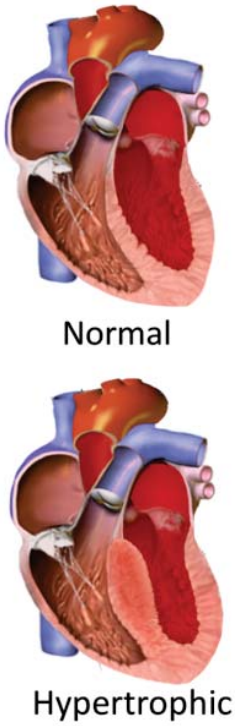


Figure 8: Note the enlargement in the muscle of the left ventricle, decreasing its size. This makes pumping blood through the heart less efficient [9].

Hypertrophic Cardiomyopathy (HCM) is a disease in which the heart muscle (myocardium), and more specifically the left ventricular wall, enlarges. The enlargement causes the left ventricle to shrink, and ultimately pump blood less efficiently as shown in Figure 8 [3].

Approximately 80% of HCM is caused by mutations in two genes that code for sarcomere proteins: beta-myosin heavy chain (MYH7) and myosin-binding protein C (MYBPC3) [4]. In order to understand how mutations in these proteins cause HCM, it is important to know the structure and function of the sarcomere.

The sarcomere is the basic unit of both cardiac and skeletal muscles. Sarcomeres are rows of alternating lines of actin and myosin. The lines of myosin include "heads" that stick out and attach to the actin, but only attach to actin when Calcium ions (Ca^{2+}) are present. When Ca^{2+} is present and myosin binds to actin, the energy stored in ATP allows myosin to pull the actin closer together, con-

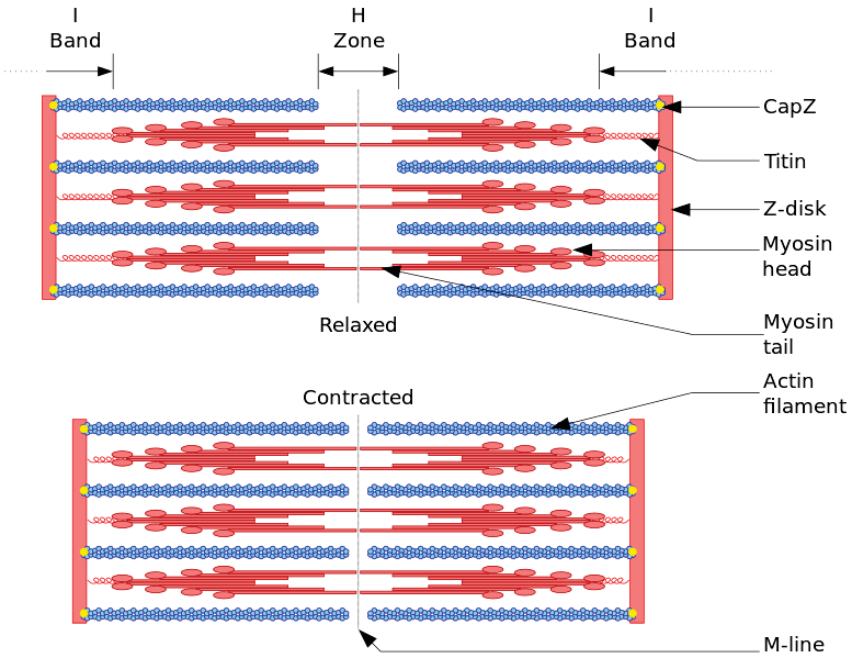


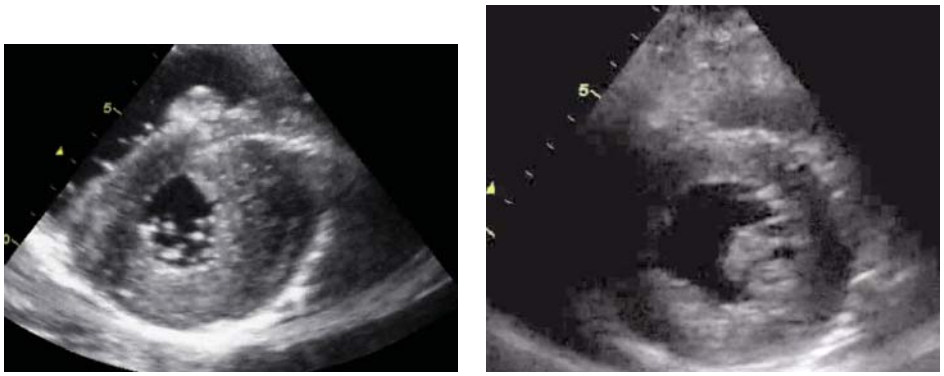
Figure 7: The contraction of the sarcomere. When Ca^{2+} is present, Myosin will cause the actin filaments to move closer together, contracting the muscle [8].

tracting the muscle as shown in Figure 7.

MYH7 and MYBPC3 encode for proteins that make up the myosin filaments in the muscle. A proposed mechanism for the pathogenesis of hypertrophic cardiomyopathy first involves the altered structure of the MYH7 or MYBPC3 myosin binding protiens due to a pathogenic vairiant in the genes MYH7 or MYBPC3, causing them to be less effective in binding to actin. This causes the myosin filament to contract less efficently, and requires the heart muscle to grow larger in order to have the same pumping effect, ultimately increasing the size of the left ventricular wall [24].

Another approximately 20% of HCM is caused by a variety of both known and unknown causes. Several other genes such as TNNT2, TPM1 and MYL3 contribute to very small percentages of HCM, but the majority of HCM cases are due to MYH7 or MYBPC3 mutations [4].

HCM is the most common congenital heart condition known, and is also the most common cause of sudden cardiac death upon exercise. The prevalence of HCM in the general population is generally agreed to be 1 in 500 (0.2%) [4]. This means that, with 1,326,836 individuals in active duty military status in June 2017 [25], over 2,500 individuals will have HCM, and over 2,000 individuals will have HCM due to a mutation in MYH7 or MYBPC3. HCM is also listed as a disqualifying condition in the military [26]. As Eckart et al. stated, sudden cardiac death is an issue in the military, especially because sudden cardiac death is thought to be brought upon by intense exercise [15]. The military therefore has great interest in exploring and preventing the most common cause of sudden cardiac death, hypertrophic cardiomyopathy (HCM). It is also important to note that, if an individual is diagnosed with HCM before sudden cardiac death (SCD) occurs, SCD



(a) Heart with HCM (b) Normal heart

Figure 9: Parasternal short axis echocardiogram midpapillary level display with HCM and a normal heart. Both hearts are shown while the left ventricle is contracted. Note the larger size of the left ventricular wall and smaller left ventricle in the HCM image [10].

can be prevented through treatment.

7.2.1 Current Methods in Screening and Treatment for HCM

Currently, the most widely used method for determining whether an individual has HCM is an echocardiogram (also known as an echo). An echocardiogram is a test that uses ultrasound to create pictures of the heart to diagnose certain structural defects that may be present.

Diagnosis of HCM usually requires an echocardiogram where the left ventricular walls are observed to be thicker than normal. The actual thickness of the walls depends on the location they are in the heart, and several different measures of wall thickness are used with varying degrees of accuracy, sensitivity and specificity. Figure 9 displays how HCM is diagnosed with an echocardiogram. The width of the left ventricular walls are measured, and if too large, HCM is diagnosed [11].

Genetic testing and Magnetic resonance imaging (MRI) are also used for the current diagnosis of HCM. If an individual suspected to have HCM shows negative or inconclusive on an echocardiogram, cardiac magnetic ressonance (CMR) imaging and genetic testing may be used as a follow-up procedure. Often, if an individual has a pathogenic variant that is known to cause HCM, they will get routine echocardiograms on a yearly or other frequent basis, to assess whether HCM develops at some point in their lives, as HCM may develop in different individuals on different timeframes [11].

Generally, individuals are only screened for HCM via echocardiogram if they have family history of the disease or are suspected to have the disease due to a cardiac event [11]. However, many cases of HCM that lead to SCD go undiagnosed because there are virtually no symptoms until the manifestation of SCD, and the disease can occur without family history.

Treatment for HCM includes the use of beta-blockers, calcium-channel blockers, as well as invasive procedures such as septal reduction (increasing the size of the left ventricle), and an implantable cardloverter-difibrillator (ICD). An ICD is a device that is implanted in the body that can detect fibrillation in the heart, and render shocks if fibrillation is detected, preventing sudden cardiac death. ICD devices are placed in individuals with a high risk of SCD, or history of fibrillation [11].

Generally, because the risk of SCD increases when individuals with HCM perform athletic activities, participation in intense competitive sports or intense physical activity is not recommended. The American Heart Association has developed a point system whereby the risk of certain activities to individuals with HCM is noted, displayed in Table 2. In the table, recreational (non-competitive) sports are categorized according to intensity level, and are guaged on a scale of 0 to 5 for eligibility, with 0 to 1 meaning HCM patients strongly discouraged from participating, 2 to 3 meaning possible participation depending on individual clinical results and severity, and 4 to 5 meaning likely permitted participation. Note that participation in competitive sports is not recommended, and that many of the activities listed as strongly discouraged from participating (such as running, etc.) are activities that individuals will participate in during military training or duties [11].

Genetic screening or testing may offer an accurate and more inexpensive method for identifying individuals that have HCM than electrocardiography. Genetic testing may or does cost less than electrocardiography. The average price billed to Medicare for echocardiography in fiscal year 2015 was $2,506 [27]. Genetic screening may cost $1,000 or less [28]. Additionally, genetic screening has the potential to uncover additional conditions in addition to HCM that echocardiography cannot detect.

Table 2: American Heart Association Recommendations for the Acceptability of Recreational (Noncompetitive) Sports Activities and Exercise in Patients With HCM [11].
Numbers from 0-1 indicate HCM patients are strongly discouraged from participating, 2-3 indicates possible participation, and 4-5 indicates likely permitted participation.

High Intensity		**Moderate Intensity**		**Low Intensity**	
Basketball	0	Baseball/softball	2	Bowling	5
Body Building	1	Biking	4	Golf	5
Gymnastics	2	Modest hiking	4	Horseback riding	3
Ice Hockey	0	Motorcycling	3	Scuba diving	0
Racquetball/squash	0	Jogging	3	Skating	5
Rock climbing	1	Sailing	3	Snorkeling	5
Running (sprints)	0	Surfing	2	Weights (nonfree)	4
Skiing	2	Swimming	5	Brisk walking	5
Soccer	0	Tennis (doubles)	4		
Tennis (singles)	0	Treadmill/stationary bicycle	5		
Football (touch/flag)	2	Weightlifting (free weights)	1		
Windsurfing	1	Hiking	3		

7.3 An Analysis of ClinVar for Pathogenic Variants of MYBPC3 and MYH7

All variants found in gnomAD for MYBPC3 and MYH7 were screened using ClinVar in October 2017 to find known pathogenic and likely pathogenic variants. Table 3 describes the results of the ClinVar analysis. As described in Section 6.3, this ClinVar analysis is likely incomplete. It is likely that many more pathogenic variants are left undiscovered by ClinVar.

Table 3: ClinVar Variants in MYH7 and MYBPC3

Gene	# of Benign Variants	# of Pathogenic Variants	Freq. of Benign Variants	Freq. of Pathogenic Variants
MYH7	203	44	2.52	5.55E-4
MYBPC3	143	46	2.75	9.47E-4

7.4 Genetic Linkage Analysis

As illustrated in Figure 5, the gnomAD database does not associate whole genomes together. Therefore, it is unknown if an individual in the gnomAD database has only one pathogenic variant, or instead has multiple pathogenic variants. Some genetic variants are usually inherited together: this is because they are close to each other on the same chromosome and are "linked:" during crossing-over in meiosis, they will almost always be inherited together. Genetic variants inherited together are known as haplotypes. To determine if haplotypes will cause genetic variants found in ClinVar to be inherited together, the 1000 genomes database was analyzed to see if co-location of genetic variants exists.

The 1000-genomes database is a database comprised of 2,504 whole genomes [29, 30]. This database allows the user to see every variant that a particular individual has, allowing for haplotype analysis. This database is too small to be used to analyze the frequency of rare variants in a general population, but may be used to see if certain variants are inherited together.

Haplotypes may, in the end, cause the number of affected individuals from the genetic screening to change. As illustrated in Figure 10, variants that are independent are measured by the gnomAD database to come from three separate individuals. However, haplotype analysis may find that all three variants are found in one individual. This may ultimatley affect the prevalence, penetrance, and cost/benefit analysis of genetic screening.

Using the 1000 genomes database version 3, in MYH7 and MYBPC3 [29], six variants that were labeled as "Pathogenic" according to ClinVar were found. (14:23888796 C/T; 14:23898247 G/A; 11:47355169 G/A; 11:47357547 G/T; 11:47364621 G/A; 11:47374186 C/G). None of these variants were found on the same genotype as any of the other

Figure 10: Haplotype analysis may allow the measured number of affected individuals to decrease.

pathogenic variants. Because of this finding, all variants used in this study are assumed to be independent of any other variants.

7.5 Parameters Used in Logistic Regression Modeling

There were five main parameters that were used in logistic regression modelling for MYH7 and MYBPC3. Each of these parameters was chosen based on its relevance in determining genetic pathogenicity, and each parameter was analyzed statistically by itself to assure that it could adequately separate known pathogenic variants from known benign variants.

Each parameter was assessed graphically using boxplots or mosaic plots. Boxplots, or "box and whisker plots" show the different percentiles of each variable. Figure 11 shows an example boxplot. A good parameter will separate pathogenic and benign variants, and will be seen as a large difference between the percentiles of the parameters between pathogenic and benign variants. Boxplots were created for the MYBPC3 gene variants alone, the MYH7 variants alone, and a dataset combining the MYBPC3 and MYH7 variants. Separation was assessed based on these three boxplots for each parameter.

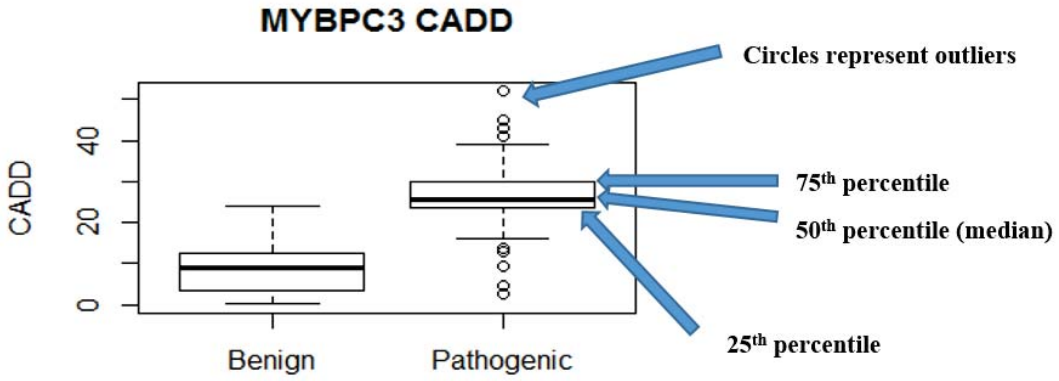


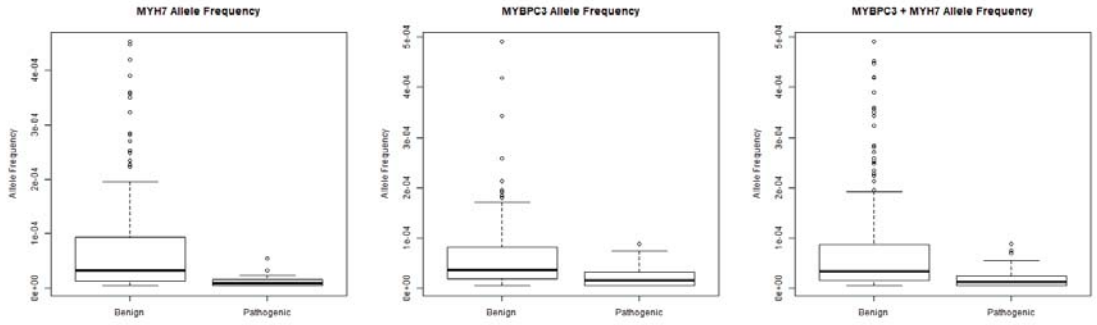
Figure 11: Example boxplot. Useful parameters will display different values for "pathogenic" and "benign" variants.

7.5.1 Parameter 1: Allele Frequency

Allele frequency is the frequency that a variant occurs in a population. In the gnomAD database, it is represented according to Equation 2.

$$Allele\ Frequency = \frac{Number\ of\ alleles\ in\ gnomAD}{Total\ gnomAD\ population} \tag{2}$$

Because genetic conditions are rare, it would be expected that alleles with lower allele frequency would be more likely to be pathogenic. This is seen in Figure 12.



(a) MYH7 only (b) MYBPC3 only (c) MYH7 + MYBPC3

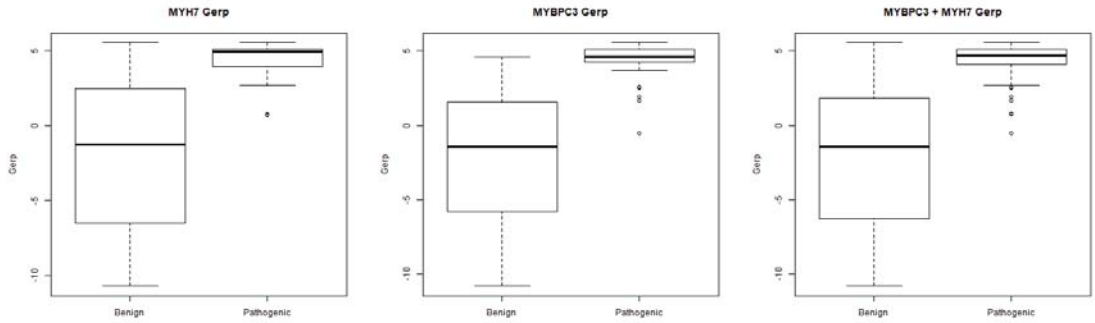
Figure 12: Boxplots of allele frequency. Benign variants have much higher allele frequencies than pathogenic variants, but the separation is not complete.

It is important to note that only variants that were of frequencies below 0.05% in the population were included in the final models. This is because variants over 0.05% frequency in the population are highly unlikely to be causative of rare genetic disease. No pathogenic variants above a frequency of 0.009% were found in ClinVar for MYH7 or MYBPC3. Because genetic disease occurs at a low frequency in the population (HCM occurs at a 0.02% frequency) [3], and almost always involves more than one variant that causes disease, the expected frequency of a pathogenic variant in the population is well below 0.05%. It was found that including variants over 0.05% in the logistic regression model caused the logistic regression model to overuse frequency as a predictor of pathogenicity, and call everything below a threshold frequency as pathogenic regardless of other parameters. Setting a cutoff frequency of 0.05% allowed other useful parameters to become relevant, as frequency exhibits a less pronounced role in the logistic regression model when all variants explored have a relatively low frequency.

Figure 12 displays the boxplots for allele frequency with a cutoff of 0.05%. It can be seen that many benign variants have a higher frequency than pathogenic variants, however the separation is not complete.

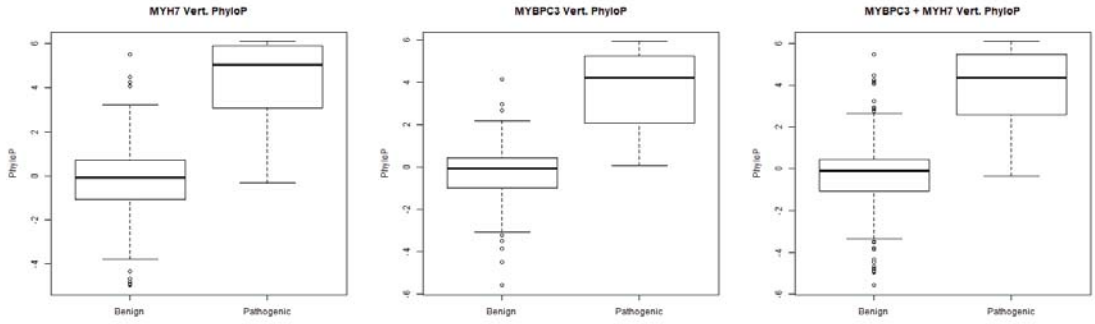
7.5.2 Parameter 2: Genetic Conservation

Genetic conservation measures how much a certain genetic location has remained the same over the course of evolution. Genetic locations that retain the same base pairs over



(a) MYH7 only (b) MYBPC3 only (c) MYH7 + MYBPC3

Figure 13: GERP variable separation. Note that pathogenic variants have a higher GERP score than benign variants, but the separation is not complete.



(a) MYH7 only (b) MYBPC3 only (c) MYH7 + MYBPC3

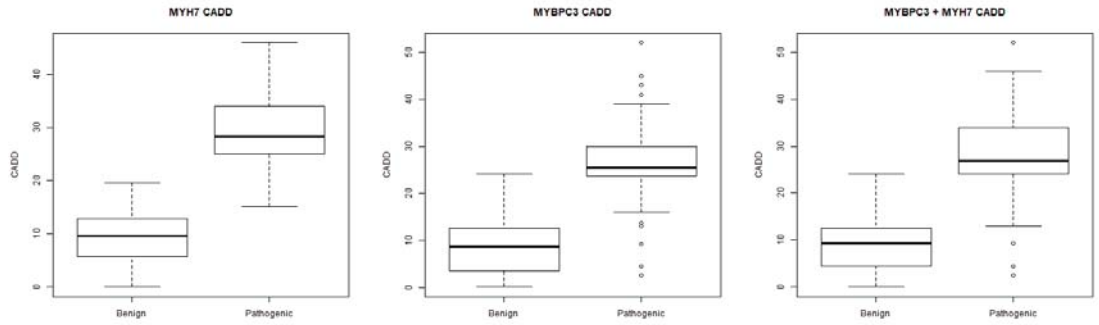
Figure 14: Vertebrate PhyloP variable separation. Note that pathogenic variants have a higher PhyloP score than benign variants, however the separation is incomplete.

a progression of many species are likely fundamental to basic organism function, because they may not confer a genetic advantage when changed. Genetic locations that change base pairs likely have functions that may not be as fundamentally important to an organism. An example of this could be a gene that codes for a cellular ionic pump that is present in all vertebrate species. Changes in base pairs in this genetic location cause organism to undergo severe metabolic disease because of the loss of function of this crucial ionic pump. This genetic location would be highly conserved over the course of evolution.

Two separate conservation scores were used in this study: the Genomic Evolutionary Rate Profiling (GERP), which looks for conserved variants in 29 mammalian species [31], and the Vertebrate PhyloP, which looks for conserved variants in 100 non-human primate species [32]. Each score was assessed independently for parameter separation. GERP is shown in Figure 13, and Vertebrate PhyloP is shown in Figure 14. Both scores provided some, yet not complete, variable separation.

7.5.3 Parameter 3: Combined Annotation Dependent Depletion (CADD)

The Combined Annotation Dependent Depletion, or CADD, is a measure of deleteriousness, or how much a variant is selected against in evolution. If a variant is at a lower frequency than would be expected according to evolution, its CADD score is higher [33]. CADD takes many different parameters, including allele frequency, genetic conservation, and protein effects, and combines them into an algorithm that predicts deleteriousness. As shown in Figure 15, CADD provides limited separation between pathogenic and benign variants.



(a) MYH7 only (b) MYBPC3 only (c) MYH7 + MYBPC3

Figure 15: CADD variable separation. Note that pathogenic variants have a higher CADD score than benign variants, but the separation is incomplete.

It is important to note that the CADD authors carried out an experiment to determine how well its measure correlated with ClinVar pathogenic variants. However, in the CADD study, they defined benign variants as any variant with an allele frequency in the general population of over 5%. This definition of benign variants, and hence benign classification, is not useful for this study. The model being built in this study looks to distinguish low-frequency pathogenic variants from low-frequency benign variants [33]. Therefore, using CADD alone to determine pathogenicity of low-frequency variants based on this study may not be the most effective tool.

7.5.4 Parameter 4: Protein Consequence

As discussed in section 1.4, genetic disease is most often caused by changes in the amino acid sequence of a protein. Protein consequence answers two different questions:

1. Does the variant change the amino acid in a protein?
2. Does the variant change the amino acid *type* in a protein/is it a conservative or nonconservative mutation?

The answer to question #1 simply rests on whether the variant causes an amino acid change. When an amino acid is changed, the likelihood of pathogenicity increases due to the chance the amino acid change may alter the protien in a damaging way. However, the answer to question #2 is related to amino acid *type*. Amino acids were grouped into six separate categories as shown in Table 4. There are many different ways to group amino

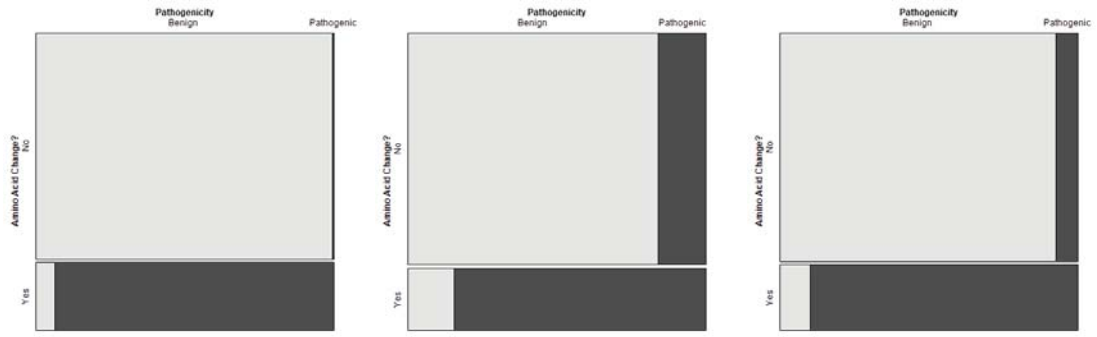
acids, according to Dagan et al. and Zhang [34, 35]. This grouping looked to differentiate amino acids based on their polarizability and aromaticity. However, many other groupings of amino acids may exist, and future studies may explore the efficacy of different groupings. If a variant did not cause an amino acid change or changed an amino acid to one in the same category, it was called a conservative mutation. If a variant caused an amino acid change to one of a different category, it was called a nonconservative mutation.

Table 4: Types of Amino Acids for Conservative Mutation Analysis

Type	Amino Acids
Positive	Arginine, Histidine, Lysine
Negative	Aspartic Acid, Glutamic Acid
Polar	Serine, Threonine, Asparagine, Glutamate, Cysteine
Aromatic	Tyrosine, Tryptophan, Phenylalanine
Nonpolar	Methionine, Glycine, Alanine, Valine, Leucine, Isoleucine, Proline

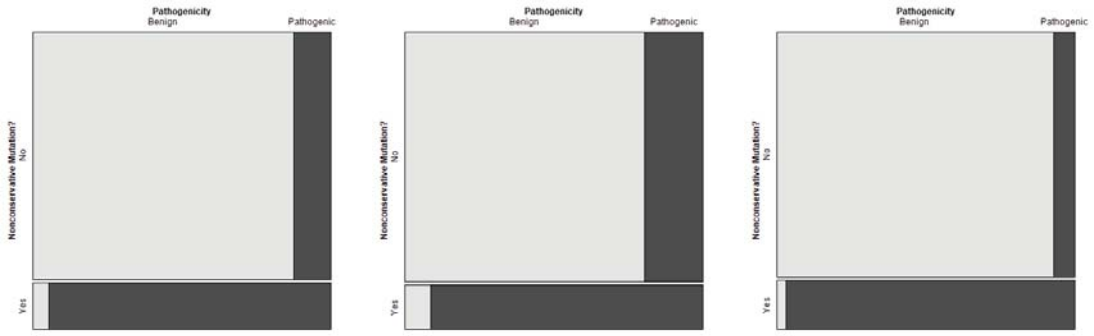
Nonconservative mutations would be expected to more likely cause genetic disease, as the structure of a protein, and hence the function, would be more likely to change if an amino acid with completely different properties replaced another amino acid.

The plots that view separation between these two parameters are shown in Figure 16 for amino acid change, and Figure 17 for conservative/nonconservative change. These mosaic plots illustrate separation by distinguishing pathogenic/benign variants as black/grey boxes, respectively. Separation can be seen for each parameter, but is not complete.



(a) MYH7 only (b) MYBPC3 only (c) MYH7 + MYBPC3

Figure 16: Amino acid change variable separation. Note that most pathogenic variants involve an amino acid change, and most benign variants do not involve an amino acid change. However, separation is not complete.



(a) MYH7 only (b) MYBPC3 only (c) MYH7 + MYBPC3

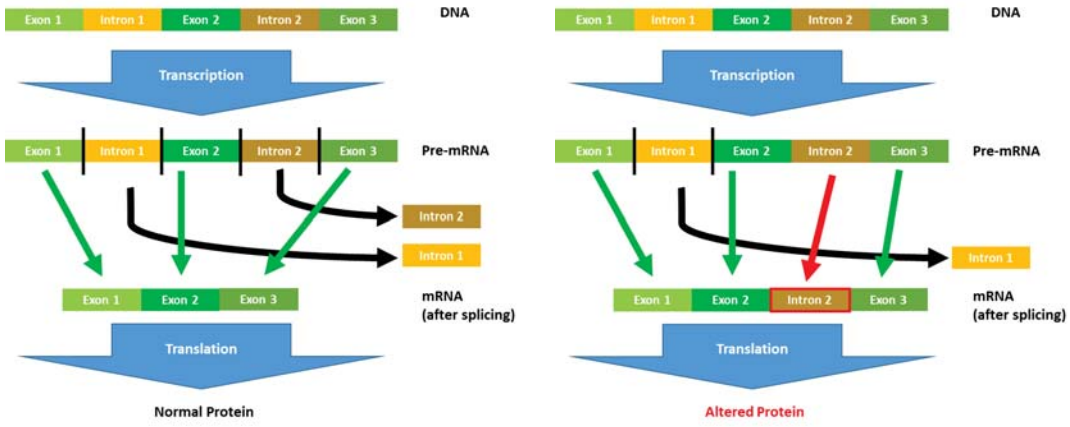
Figure 17: Conservative/nonconservative mutation variable separation. Note that most pathogenic variants involve a nonconservative amino acid change, and most benign variants involve a conservative amino acid change or no amino acid change. However, separation is not complete.

7.5.5 Parameter 5: Splice Site Pathogenicity

Genes include regions known as introns and exons. Introns are regions of genetic code that are not translated into protein. Exons are regions of genetic code that are translated into protein. However, RNA polymerase translates both of these regions into mRNA from DNA. Therefore, before the mRNA is translated into protein, the introns in the mRNA are removed in a process known as splicing. This is shown in Figure 18a. If mutations occur in the splice site, errors in splicing can cause introns to be inserted or exons to be removed, as illustrated in Figure 18b, which ultimately will effect protein structure and may cause disease.

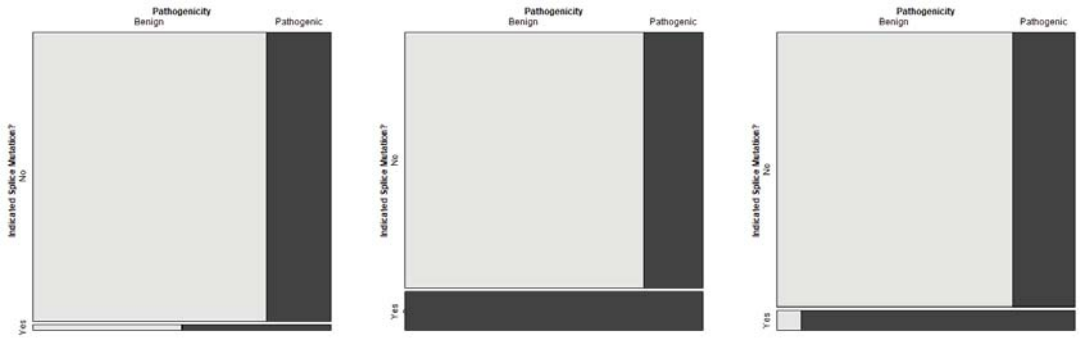
Originally, a separate predictor for splice site variants was not to be used in the model. However, a majority of the incorrectly classified genetic variants according to models without the predictor for splice site variants were splice site variants. We then incorporated the database of single nucleotide variants within splicing consensus regions (dbscSNV) into the model. dbscSNV is a database produced by Jian *et al.* that uses eight splicing disease predictors and correlates them with genome-wide pathogenicity databases [36]. It ranks splice sites on the likelihood of being pathogenic from 0 (most likely benign) to 1 (most likely pathogenic).

It is important to note that the dbscSNV database only includes values for splice site variants. Exonic or other non-splice site intronic regions do not have a dbscSNV score. To incorporate this into the model, a value of "1" was given for a dbscSNV score at or above 0.6, and a value of "0" was given to a dbscSNV score below 0.6 or if a dbscSNV score was not recorded for a variant. Figure 19 shows the variable separation between pathogenic and benign variants for the dbscSNV score. Note how in Figure 19, indicated splice site mutations include mostly pathogenic variants. However, many pathogenic variants are left out of the predictor.



(a) Normal splice site (b) Altered splice site

Figure 18: Splicing occurs between Pre-mRNA and mature mRNA after splicing. It removes introns from the pre-mRNA transcript and assembles exons together, which are then used to create a protein. Figure 18a shows how a splice site operates normally, and Figure 18b shows an altered splice site and its potential effects. In the altered splice site, a splice site mutation causes intron 2 to be left in the final mRNA transcript, which causes altered protein structure.



(a) MYH7 only (b) MYBPC3 only (c) MYH7 + MYBPC3

Figure 19: Variable Separation for the splice indicator parameter. Note that although it does not distinguish pathogenicity among all variants well, it selects splice site variants that are pathogenic that would have been classified as benign without previous analysis.

7.5.6 Overview of Parameters

A brief summary of the parameters used:

1. Allele Frequency: how common is the allele in the population?
2. Genetic Conservation: how much has the genetic location remained the same over the course of evolution?
3. CADD: how much is the variant selected against over evolution?
4. Protein consequence: how does the variant change the protein?

5. Splice site indication: is the splice site affected in a way that may alter the protein?

Each of these parameters distinguish between pathogenic and benign variants in MYH7 and MYBPC3, however do so incompletely. This indicates that each parameter may be useful in a logistic regression model, yet the final logistic regression model will likely require more than one parameter to best separate the variables.

7.6 Creating and Optimizing the Logistic Regression Models

The statistical software R was used to create three sets of 128 independent logistic regression models that each used a different set of parameters. The R package MuMIn was used with the function dredge() to attain all possible combinations of parameters [37]. However, models were selected to reduce "double-dipping," or counting the same parameter twice. Because GERP and Vertebrate PhyloP (VerPhyloP) each measured conservation, models that used both GERP and VerPhyloP were excluded. CADD also used GERP and VerPhyloP in its own model calculations, and so models that included GERP or VerPhyloP with CADD were also excluded. The three sets of data used for the logistic regression models were MYBPC3 variants alone, MYH7 variants alone, and MYBPC3 and MYH7 variants together.

7.6.1 The Akaike Infromation Criterion

The Akaike Information Criterion (AIC) was used to determine the "best" model of the 128 models tested. Equation 3 gives the formula for the AIC. The AIC is composed of two different factors: the likelihood ($\hat{L}$) and the number of parameters (k). The likelihood is an indicator of how well the model fits the training data. If the model is a better predictor of the pathogenicity of the ClinVar known pathogenic or known benign variants in MYH7 or MYBPC3, the likelihood will increase. This will, in turn, cause the AIC to become lower.

The second factor (k) is a penalty for additional parameters: the more parameters included in the model, the larger the penalty. This prevents the model from overfitting. Overfitting occurs when a model includes so many parameters that it fits the training data well, but does not generalize to other datasets well. To prevent this, unnecessary parameters are penalized in the AIC. Ultimately, a lower AIC is considered a "better" model. However, the AIC is just one of many factors that must be taken into account in order to determine which model is the best. The parameters used must also be taken into account to see if one model makes sense more than another. An example of this may be a model that uses two redundant parameters: two parameters that measure almost the same thing. Even though the addition of one may improve the model's fit marginally, it will not significantly improve the model enough for the addition of the second parameter to be useful.

$$AIC = -2ln(\hat{L}) + 2k \tag{3}$$

7.6.2 Running the Models

Each of the 128 models were run using R and the AIC was recorded for each. 64 of the 128 models fit the criteria of not including CADD with Gerp or Vertebrate PhyloP, and

Table 5: Top 5 Models According to AIC

Model #	Allele Frequency	Gerp	CADD	Splice Indicator	Vertebrate PhyloP	AA Change?	Conservative Change?	MYH7 Rank	MYBPC3 Rank	MYBPC3 + MYH7 Rank	Total Rank Number	Rank
46	■		■	■		■		5	4	1	10	1
122	■		■		■	■	■	11	2	3	16	2
44	■	■		■		■		4	9	4	17	3
45			■	■		■		2	10	6	18	4
110	■		■	■		■	■	10	7	2	19	5

not including Gerp and Vertabrate PhyloP together. "Running" models means executing R statistical software code while the R program performs machine learning to fit a model. Models were ranked by AIC for each of three separate datasets: for MYBPC3 variants alone, MYH7 variants alone, and MYBPC3 and MYH7 variants together. The "best" model was determined by finding the model that on average performed the best on each dataset by adding up the AIC ranking of the model from each dataset. The top 5 models are shown in Table 5, and all 64 models are shown in Supplementary Table S1. A parameter filled in black in the table indicates that the parameter was used in the model.

As shown by Table 5, the actual models that have the lowest AIC for each dataset differ. This indicates that the parameters for each gene give slightly different indicators of pathogenicity, and indicates that generalizing a model to fit all genes may be less accurate than generalizing a model to fit fewer genes or a single gene.

The model that appears to generalize best according to all three datasets was found to be model #46, which includes the parameters allele frequency, CADD, splice indicator, and amino acid change. This model was used to predict variants that are pathogenic but not found in ClinVar further in this study.

7.6.3 Setting the Cutoff

The "cutoff" is a value that, when the model returns a value greater than for a specific variant, the variant will be classified as "pathogenic." To find the most appropriate value for the cutoff, a Receiver Operatic Characteristic (ROC) curve was used. The ROC curve plots True Positive Rate (TPR, also known as the sensitivity; Equation 4) against False Positive Rate (FPR; Equation 5).

$$TPR\ or\ Sensitivity = \frac{Pathogenic\ variants\ identified\ by\ model}{Total\ actual\ pathogenic\ variants} \tag{4}$$

The true positive rate increases when the model becomes better at identifying if an actually pathogenic variant is pathogenic. If the model identifies every actual pathogenic variant as "pathogenic," the TPR will be an ideal value of 1. The TPR will always be 1 if a cutoff for calling a variant pathogenic occurs at 0% chance of pathogenicity, and will always be 0 if a cutoff for calling a variant pathogenic occurs at 100% chance of pathogenicity.

$$FPR = \frac{Pathogenic\ variants\ identified\ by\ model\ but\ NOT\ actually\ pathogenic}{Total\ variants\ actually\ NOT\ pathogenic} \quad (5)$$

The false positive rate increases when the model becomes worse at distinguishing which variants are benign, or not pathogenic. If the model identifies every benign variant as not pathogenic, the FPR will be an ideal value of 0. The FPR will always be 0 if a cutoff for calling a variant pathogenic occurs at 0% pathogenicity, and will always be 1 if a cutoff for calling a variant pathogenic occurs at 100% pathogenicity.

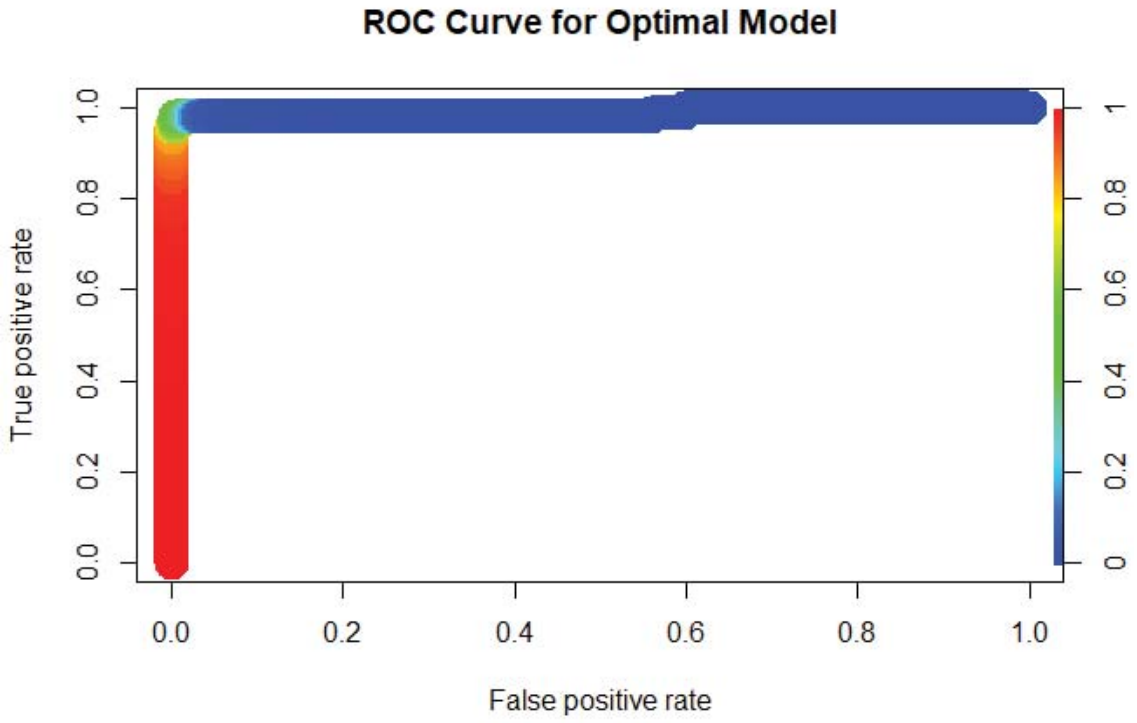


Figure 20: ROC curve for Optimal Model (model #46). FPR and TPR are maximized at a cutoff of around 0.7

An ROC curve plots TPR vs. FPR for a given model cutoff. The model cutoffs on the ROC curve are shown as different colors. In the case of Figure 20, which is an ROC curve for the optimal model using the combined MYH7+MYBPC3 variant dataset, red

represents a frequency cutoff of $\sim 100\%$ pathogenicity, yellow represents a frequency cutoff of $\sim 75\%$ pathogenicity, green represents a frequency cutoff of $\sim 50\%$ pathogenicity, and dark blue represents a frequency cutoff of $\sim 0\%$ pathogenicity. The ideal cutoff will maximize TPR while minimizing FPR, and can be found in the upper left corner of the ROC curve. In this case, a frequency cutoff of $\sim 70\%$ pathogenicity was chosen that maximized TPR (~ 0.95) and minimized FPR (~ 0.01). This means that for this model and this cutoff, the model was able to detect $\sim 95\%$ of the known pathogenic variants, and only called $\sim 1\%$ of the known benign variants pathogenic.

7.6.4 Cross-Validation: Sensitivity and Specificity

Table 6: Cross-Validated Model Performance, Cutoff = 0.7

	Variants Classified by model as pathogenic	**Variants Classified by model as benign**
Actually Pathogenic Variants (ClinVar)	85	5
Actually Benign Variants (ClinVar)	1	345

Once a cutoff has been set, the model has been successfully "trained," and created optimally to predict undiscovered pathogenic variants in MYH7 and MYBPC3. However, in order to assess how well the model performs with regard to *new* data, we perform cross-validation. Because our dataset is so small, we perform leave-one-out cross-validation.

Traditional validation techniques normally use partitioning of data into two random sets: a training dataset (70% of data) and a testing dataset (30% of data). The training dataset is used to *create* the model, and then the testing dataset is used to see how the model performs on new data that the model was not trained on. However, because of our limited dataset size which includes only 90 pathogenic variants, we believe that partitioning data into these two datasets may cause the testing dataset to lose modeling capability.

Leave-one-out cross-validation (LOOCV) is a statistical technique that allows all of the data to be used as a training set (this is what is described in the previous sections by creating the model). However, LOOCV allows us to explore how well the model we create performs on new data. LOOCV works by taking all of the data and removing one datapoint (in this case, one variant). A new model is created and trained with the remaining datapoints, and the datapoint "left out" is predicted based off of the model created from the other datapoints. This process is repeated, leaving every single datapoint in the dataset out and creating the same number of models as datapoints. The model prediction for each datapoint "left out" is used to validate the model.

We used a cutoff of 0.7 and used LOOCV to validate the model we created to predict variant pathogenicity in MYH7 and MYBPC3. The results of this validation are displaed in Table 6. From these results, we can determine the sensitivity and specificity of this model validation. The sensitivity is the same as the true positive rate (TPR; defined in

Equation 4) and determines the proportion of correctly identified positives. The specificity, or the true negative rate, measures the proportion of correctly identified negatives and is defined in equation 6.

$$Specificity = \frac{Total\ variants\ actually\ NOT\ pathogenic}{Total\ variants\ identified\ by\ model\ as\ NOT\ pathogenic} \tag{6}$$

Having a high sensitivity indicates that the model will find most people with disease. Having a high specificity indicates that the model will not flag people as diseased when they actually do not have disease.

Table 6 illustrates that 85 variants were correctly identified as pathogenic by the model, and five variants that were actually pathogenic were classified as benign. This indicates a sensitivity of $85/90 = 94.4\%$. Additionally, 345 variants were correctly classified as benign, and one variant that was classified as pathogenic was actually benign. This indicates a specificity of $345/346 = 99.7\%$. Based on the sensitivity and specificity results from this model, we conclude that this model performs well in predicting the pathogenicity of variants, without overclassifying variants as pathogenic.

8 Methods of Cost/Benefit Analysis

In order to determine how effective genetic screening may be in the military, a cost/benefit analysis was performed. The cost/benefit analysis attempted to determine the monetary cost and benefit of the implementation of genetic screening and other HCM screening methods in military populations in addition to the effectiveness of the tests as screening tools. This was done through producing a multi-step simulation. However, several limitations exist for this analysis. The cost/benefit analysis does not directly account for capital costs that may be required to initiate genetic screening or any other type of screening in the military population, additional strain on the healthcare system, or the psychological impact of a false positive result. This cost/benefit analysis looked to analyze the cost and benefit of the implementation of genetic screening, and other screening tests, for Hypertrophic Cardiomyopathy in the military population using only the genes MYBPC3 and MYH7. Other conditions and genes were not included in the simulation, however a discussion on how additional conditions or the inclusion of additional genes may alter the cost/benefit numbers is included in Section 13.

This cost/benefit analysis compared six different cases, or six different scenarios in which individuals with HCM are screened for. For each case, the cost of the screening, as well as the cost of the resulting deaths due to SCD from HCM were recorded. The six cases compared are outlined in Table 7.

Table 7: Cases Being Compared in Cost/Benefit Analysis

Case 1	No screening for HCM implemented
Case 2	Echocardiogram screening only, maximum accuracy settings
Case 3	Genetic screening followed by echocardiogram screening for positive genetic test, maximum accuracy settings
Case 4	Echocardiogram screening only, maximum specificity settings
Case 5	Genetic screening followed by echocardiogram screening for positive genetic test, maximum specificity settings
Case 6	Genetic screening only

8.1 Simulation of HCM in a Military-like population

Before monetary costs are brought into the picture, it is necessary to simulate exactly how genetic screening would perform in detecting individuals with HCM that will die of SCD during their military carrer. To do this, a simulation was created that models HCM in a real-life military population.

Ultimately, these simulations look to answer the following questions that are unrelated to costs:

1. Which individuals have a pathogenic variant for HCM?
2. Which individuals actually have HCM?

3. Which individuals that have or do not have HCM have or do not have a pathogenic variant?

4. Which individuals that have HCM will die of sudden cardiac death (SCD) during thier military careers?

5. How many individuals with or without HCM were identified by screening tests in cases 1-6?

6. Which individuals that died from SCD were identified by screening tests?

Figure 21 gives an overview of how the simulation will operate. First, a population of genomes will be created, and a population of individuals that have pathogenic variants in the population will be identified. Then, individuals will be assigned as "having HCM" or "not having HCM" based on the presence of a pathogenic variant in their genome (there will be a certian probability that an individual with a variant will have HCM, and a certain probability that an individual without a variant will have HCM). The six different screening cases will then be simulated. Finally, the simulation will determine which individuals with HCM will die of sudden cardiac death (SCD) throughout their military career.

The "genome simulation" in figure 21 will be explained in sections 8.1.1 and 8.1.2. The "disease simulation" will be explained in section 8.1.3. The "Sudden Cardiac Death" simulation will be explained in section 8.1.4, and the screening cases will be explained in sections 8.3, 8.2, and 8.6.

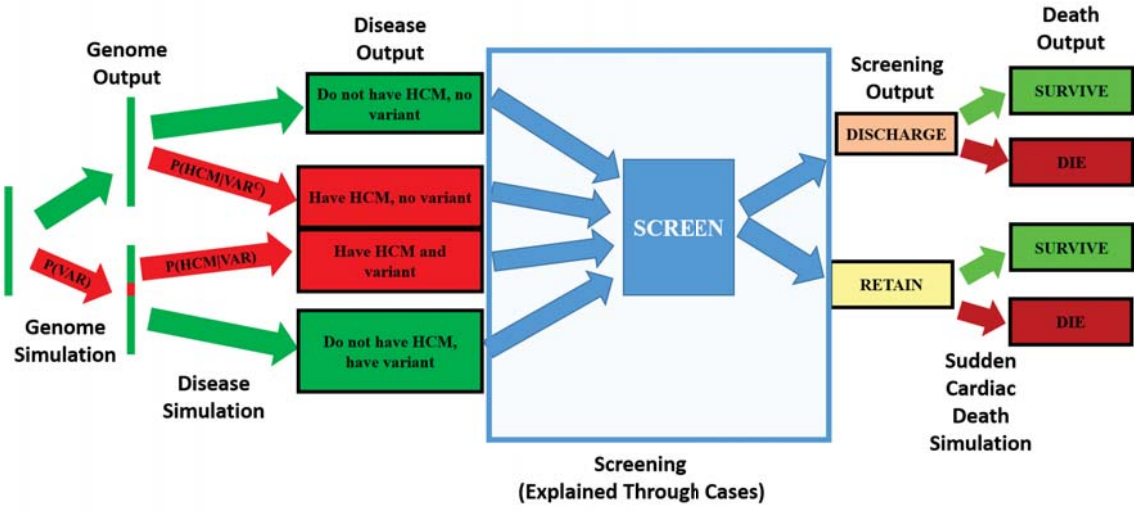


Figure 21: Overview of simulation

8.1.1 Predict Which Variants cause HCM

ClinVar and the model created in section 7 serve to determine which variants will most likely lead to hypertrophic cardiomyopathy (HCM).

With a cutoff of 0.7, set by using the ROC curve, the model classifies 1,272 variants as pathogenic, and 1,184 of those variants were not found in ClinVar. There were 4,654 variants found in the gnomAD database for these two genes, which means 27.4% of variants are classified as "pathogenic" by the model. The total frequency of all variants classified as pathogenic is 1.9% of the population (assuming all variants are independently present in individuals as determined in section 7.4). This means that if all pathogenic variants were used in a screening test, 1.9% of the population would be classified as having a pathogenic variant.

Because no data exists to prove or disprove the pathogenicity of the 1,184 variants the model classified as pathogenic but were not found in ClinVar, it cannot be assumed that the pathogenic variants according to the model are either completely pathogenic or completely benign.

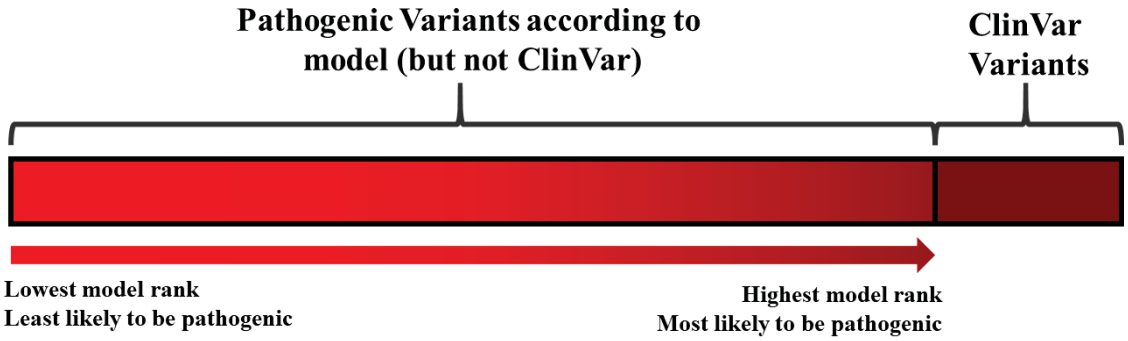


Figure 22: Variants are ranked according to their presence in ClinVar and their model score. Those variants found in ClinVar have the highest ranking (on the right), and variants found to be pathogenic according to the model are ranked based on their model score, with the higest model score ranking below the last ClinVar variant, and the lowest model score having the lowest ranking.

To address this uncertainty, a "ranked-order list" of variants was created. This rank order list consisted of all variants classified by the model as pathogenic and all of the variants classified as pathogenic by ClinVar (regardless of their model score). The list was ranked based off of the estimated likelihood that a variant may cause HCM. The highest 90 ranked variants were the variants that, regardless of their model score, were classified by ClinVar as pathogenic. These first 90 variants are considered to have equal ranking. The next variants on the list consist of the variants classified by the model as pathogenic, but not classified by ClinVar as pathogenic. These variants are ordered on the list based off of their model score, with the highest model score being the highest ranking variant (closest to the ClinVar variants), and the lowest model score being the lowest ranking variant (farthest away from the ClinVar variants). Figure 22 shows an illustration of how these variants were ranked.

This ranked variant list was used in the cost-benefit analysis to determine which variants to classify as pathogenic. In the analysis, a range of "rank cutoffs" were used, with all variants ranked higher than the cutoff being called pathogenic. This is illustrated in Figure 23.

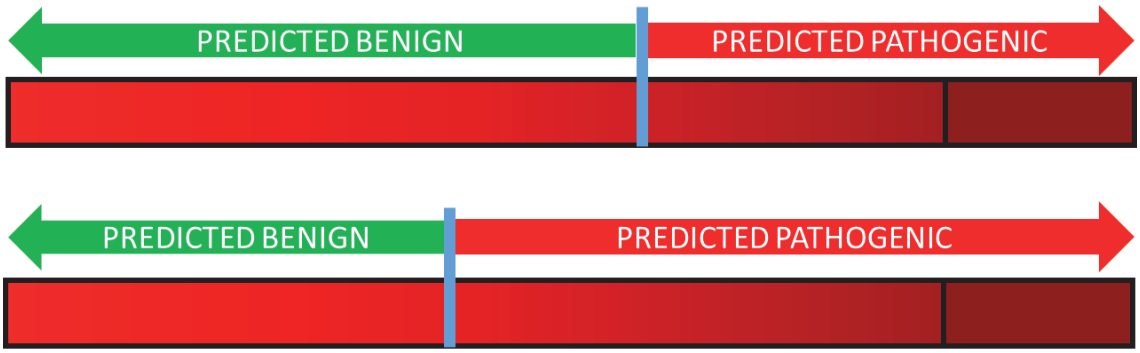


Figure 23: The ranked variant system allows the classification of pathogenic variants to be varied for the cost/benefit simulations. A cutoff may be set at any point along the ranked variant list, and all variants ranked above that cutoff will be classified as pathogenic.

8.1.2 Determining Variation of Pathogenic Variants in Populations

Once a list of variants has been determined, populations of individuals that have the variants must be created.

Although the gnomAD database gave a frequency in the gnomAD population of a particular pathogenic variant, the confidence and variation in this number among different populations is an important consideration in discussing the cost/benefit analysis of genetic screening. GnomAD is a fixed population of individuals with a fixed frequency per variant. However, it is likely that different populations will randomly have different ranges of frequency of the variants. To account for this and to assess the variation in the ultimate frequency of pathogenic variants in a general population, simulations were performed according to the steps below and Figure 24.

1. Take genome with reference variants: this genome will have all reference, or common benign variants.

2. Using the frequency of each individual pathogenic variant found in gnomAD, simulate the number of pathogenic variants that will be in the genome. In the genome in Figure 18, genetic location #2 has a 5% chance of a T $\rightarrow$ G pathogenic variant occurrence, genetic location #4 has a 0.02% chance of a C $\rightarrow$ T pathogenic variant occurrence, and genetic location #8 has a 0.01% chance of a T $\rightarrow$ C pathogenic variant occurrence.

3. As discussed in section 8.1.1, a range of cutoffs are being set for pathogenic variants on the ranked variant list. However, in the case of this analysis, a population of genomes will be created first that contains all 1,276 variants on the ranked variant list. After this population is created, the cutoff will be set, and the frequency of individuals with the particular variants of interest will be found as a part of this total population. This frequency is the number that will be used in the simulations moving forward. This allows the range of selected cutoffs to be performed on the *same* population of genomes, which is important for comparative analysis of how each cutoff performed.

4. Did any pathogenic variants (according to the cutoff) show up in the simulated genome? In the first case in Figure 24, no pathogenic variant occurred in the simulated genome.

5. Repeat this simulation carried out in steps 1-4 many times equal to the average population of military accessions to attain a figure for the military population.

6. Calculate the frequency of selected pathogenic variants in the genomes of this simulated population. In the case of the population simulated in Figure 24, 1/10 individuals, or 10% of the population, has a pathogenic variant.

7. Simulate many (1,000) populations using steps 1-5 to attain a distribution of the frequency of variants in populations. This set of populations will be used further in the cost/benefit analysis to come up with a distribution of costs that will vary for different random populations.

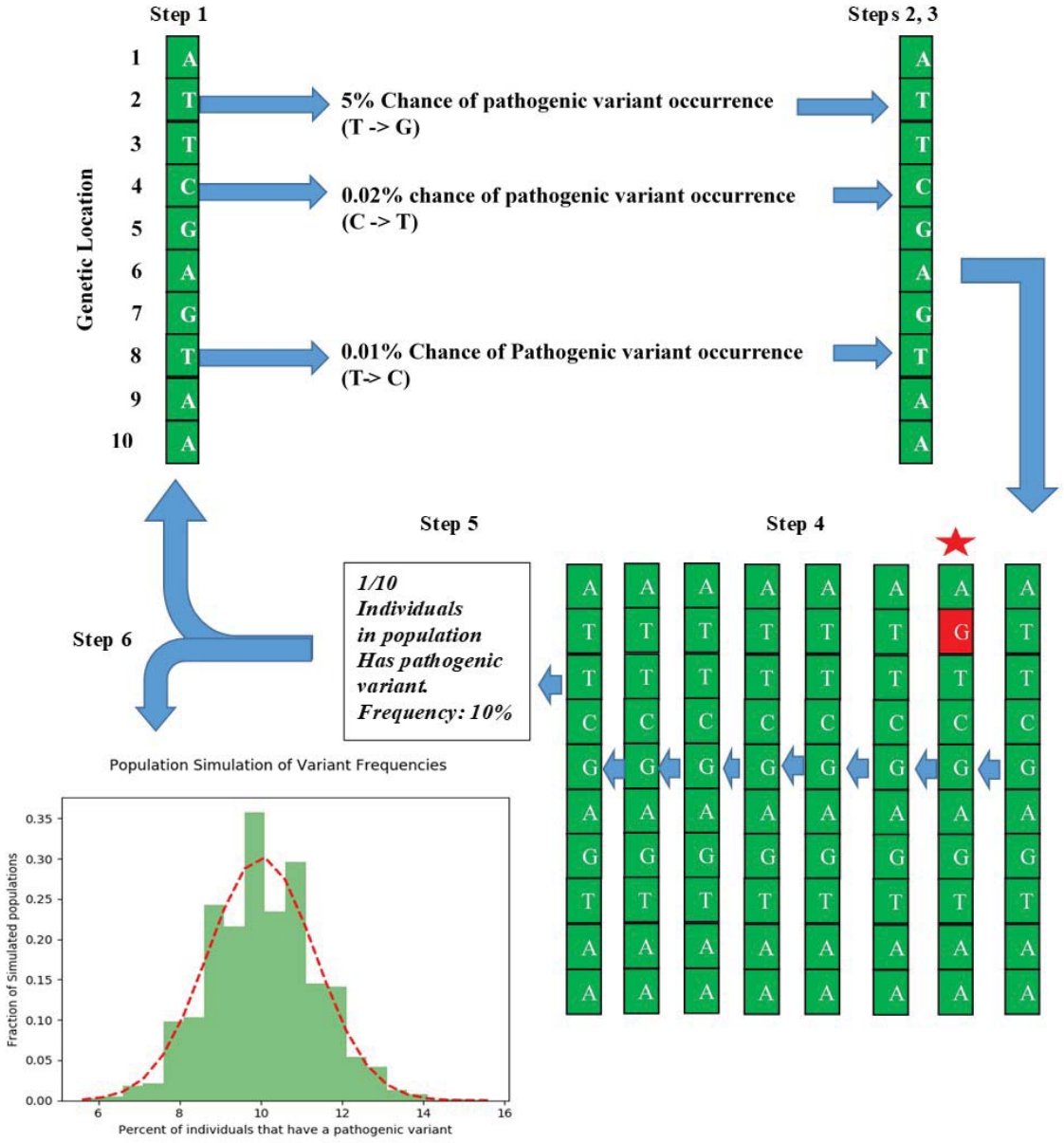


Figure 24: Simulation of populations. Certain locations in the reference genome have independent chances of being pathogenic for each individual. For each population, the frequency of individuals with a pathogenic variant was calculated. For a large number of random populations, the frequency of pathogenic variants in each population should have a range of values. Populations and genomes in this figure are not to scale.

8.1.3 Predicting HCM from Genetic Makeup

After populations of individuals have been created that have or do not have pathogenic variants, it will be determined if an individual has HCM. As stated previously, having a pathogenic variant does not guarantee that an individual will have disease, and not having a pathogenic variant does not guarantee that an individual will not have disease. This is due to the many multivariable causes of disease that include different genes, unknown variants, and environmental factors. However, having a variant may greatly increase the chances that an individual has disease.

Since we already know which individuals have a pathogenic variant and which individuals do not have a pathogenic variant from procedures in sections 8.1.1 and 8.1.2, to simulate which individuals have HCM and which do not, the probability that an individual will have HCM if they have a variant, $P(HCM|VAR)$, and the probability that an individual will have HCM if they *do not* have a variant, $P(HCM|VAR^C)$, need to be calculated. The probability that an individual will have HCM if they have a variant, $P(HCM|VAR)$, is also known as the penetrance. The penetrance can be found through literature for most known variants in ClinVar [5], however for undiscovered variants, the penetrance may have a very wide range of values. Additionally, the value of $P(HCM|VAR^C)$ was not found in literature. Because of these uncertainties, we did not set a value for $P(HCM|VAR)$ directly. Instead, we calculated $P(HCM|VAR)$ and $P(HCM|VAR^C)$ based off of equations 7 and 8 using Bayes' theorem.

$$P(HCM|VAR) = \frac{P(HCM)P(VAR|HCM)}{P(VAR)} \tag{7}$$

$$P(HCM|VAR^C) = \frac{[1 - P(VAR|HCM)]P(HCM)}{1 - P(VAR)} \tag{8}$$

There are three values that must be found in order to use these equations:

1. $\boldsymbol{P(HCM)}$: this is the probability of having HCM in the general population. This was found through the literature to be 1 in 500 individuals (0.002) [3].

2. $\boldsymbol{P(VAR)}$: This is the probability of having a pathogenic variant in the general population. This was found by setting a cutoff for the ranked variant list discussed in 8.1.1, and adding up all of the gnomAD frequencies of the pathogenic variants on the ranked variant list below the selected cutoff. The resulting frequency was $P(VAR)$.

3. $\boldsymbol{P(VAR|HCM)}$: This is the probability of having a pathogenic variant as classified by our ranked variant list given that someone has HCM. The literature agrees that for *all variants* in MYH7 and MYBPC3, this value is 0.8; or, that 80% of individuals with HCM will have a pathogenic variant in MYH7 and MYBPC3 [4]. However, we cannot assume that $P(VAR|HCM) = 0.8$ will be the value that our screening test will perform at because the ranked variant list built by the model may miss some pathogenic variants. We chose to vary this number from 0.5 to 0.9 to give a range of possible values. A value of $P(VAR|HCM) = 0.5$ indicates that if an individual has HCM, there is a 50% chance that they will have a pathogenic

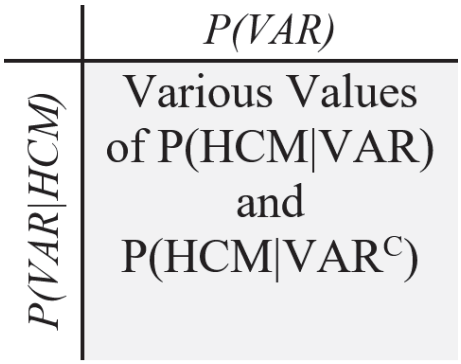


Figure 25: Calculating $P(HCM|VAR)$ and $P(HCM|VAR^C)$. $P(VAR)$ is modified through changing the cutoff of the ranked variant list, and different values of $P(VAR|HCM)$ are used from 0.5 to 0.9.

variant *as classified by our ranked variant list AND below the cutoff we set on that list*. We vary this number to see how it will affect the cost and benefit of genetic screening in the military.

As noted above, in these calculations, only $P(HCM)$ will remain constant. $P(VAR)$ and $P(VAR|HCM)$ will both vary for different cutoffs set in the ranked variant list, and different values of $P(VAR|HCM)$ being chosen. Therefore, the values of $P(HCM|VAR)$ and $P(HCM|VAR^C)$ will also vary for these two values. This is shown in Figure 25.

We chose at the beginning of this simulation to see how plausible different rank cutoffs in the ranked variant list were. We calculated, from a certain rank cutoff on the ranked variant list, $P(VAR)$, $P(HCM|VAR)$, and $P(HCM|VAR^C)$ for varying values of $P(VAR|HCM)$. Forward, the "$\#\ of\ variants$" in the simulation refers to the number of variants that are included in the simulation from the rank cutoff list. For example, a $\#\ of\ variants = 100$ indicates that the first 100, and only the first 100, variants on the ranked variant list were classified as pathogenic and causing HCM.

First, we made sure that the values of $P(HCM|VAR)$ were plausible. We calculated $P(HCM|VAR)$ for rank cutoffs from 90 to 1,276 (the entire length of the ranked variant list. The penetrance, another name for $P(HCM|VAR)$, was found empirically in studies to be approximately 0.7, meaning that 70% of individuals who have a known ClinVar pathogenic variant actually have HCM [5]. However, the penetrance may be different for different variants, and the penetrance of undiscovered variants uncovered by the model may be lower than those of discovered pathogenic variants in ClinVar. However, a penetrance below $P(HCM|VAR) = 0.3$ is not probable, as it is much lower than the values found empirically. Values of $P(HCM|VAR)$ below 0.3 were not considered realistic. Additionally, a $P(HCM|VAR)$ that is too high (0.8 and above) is less probable as well, and a $P(HCM|VAR)$ that is calculated to be greater than 1 is statistically impossible.

From the analysis of different possible values for the $\#\ of\ variants$ and $P(VAR|HCM)$, we found that $P(HCM|VAR)$ increased with an increased value of $P(VAR|HCM)$ and a decreased $\#\ of\ variants$. It was found that some scenarios with a low $\#\ of\ variants$ and a high $P(VAR|HCM)$ had a $P(HCM|VAR)$ that exceeded 1, and a large $\#\ of\ variants$ (over 400) caused $P(HCM|VAR)$ to be below 0.3. This is illustrated in Figure 26. It was

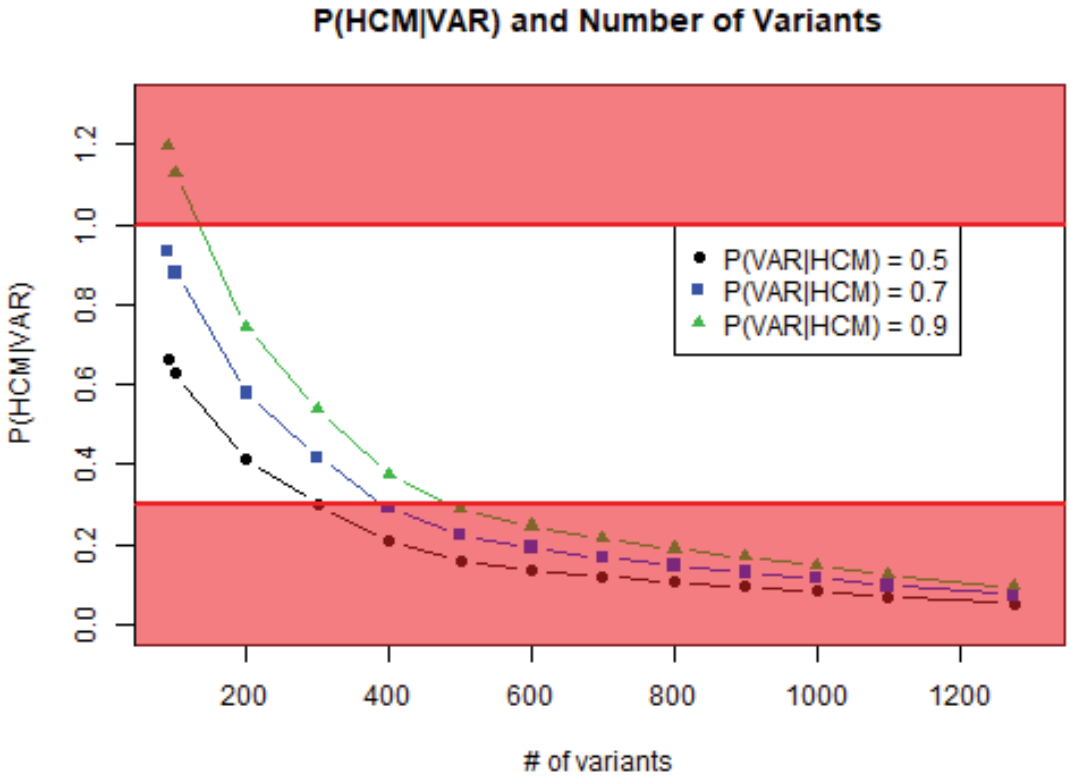


Figure 26: $P(HCM|VAR)$, or penetrance, plotted against the number of variants included from the ranked variants list. a $P(HCM|VAR)$ below 0.3 and above 1 was considered unrealistic. Due to this, the maximum number of variants included from the ranked variant list in the simulations will be 400, as a ranked variant list of length 400 gives a $P(HCM|VAR)$ of approximately 0.3 for an intermediate value of $P(VAR|HCM) = 0.7$ (with the values of $P(HCM|VAR)$ increasing for larger values of $P(VAR|HCM)$).

decided that the intermediate value of $P(VAR|HCM)$ of 0.7 would decide where to set the maximum number of variants allowed in the simulation. The value of $P(HCM|VAR)$ was 0.3 at approximately when $P(VAR|HCM) = 0.7$ and the $\#\ of\ variants = 400$. Because of this, the maximum number of variants included in the simulation from the ranked variant list was 400. In the simulation, values for the $\#\ of\ variatns$ of 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 300, and 400 variants were used; and values of 0.5, 0.55, 0.6, 0.65, 0.7, 0.75, 0.8, 0.85 and 0.9 for $P(VAR|HCM)$ were used, excluding combinations where the $P(HCM|VAR) > 1$. 119 total combinations resulted.

From this analysis, it can be seen how $P(HCM|VAR)$ varies with changing $\#\ of\ variants$ and $P(VAR|HCM)$. Figure 27 illustrates how $P(HCM|VAR)$ changes.

From the calculated $P(HCM|VAR)$ and $P(HCM|VAR^C)$, the simulation may continue and may assign individuals as having HCM or not having HCM. The simulation will assign individuals as having a pathogenic variant or not having a pathogenic variant through the methods in section 8.1.1 and 8.1.2. Figure 21 shows how the probabilities

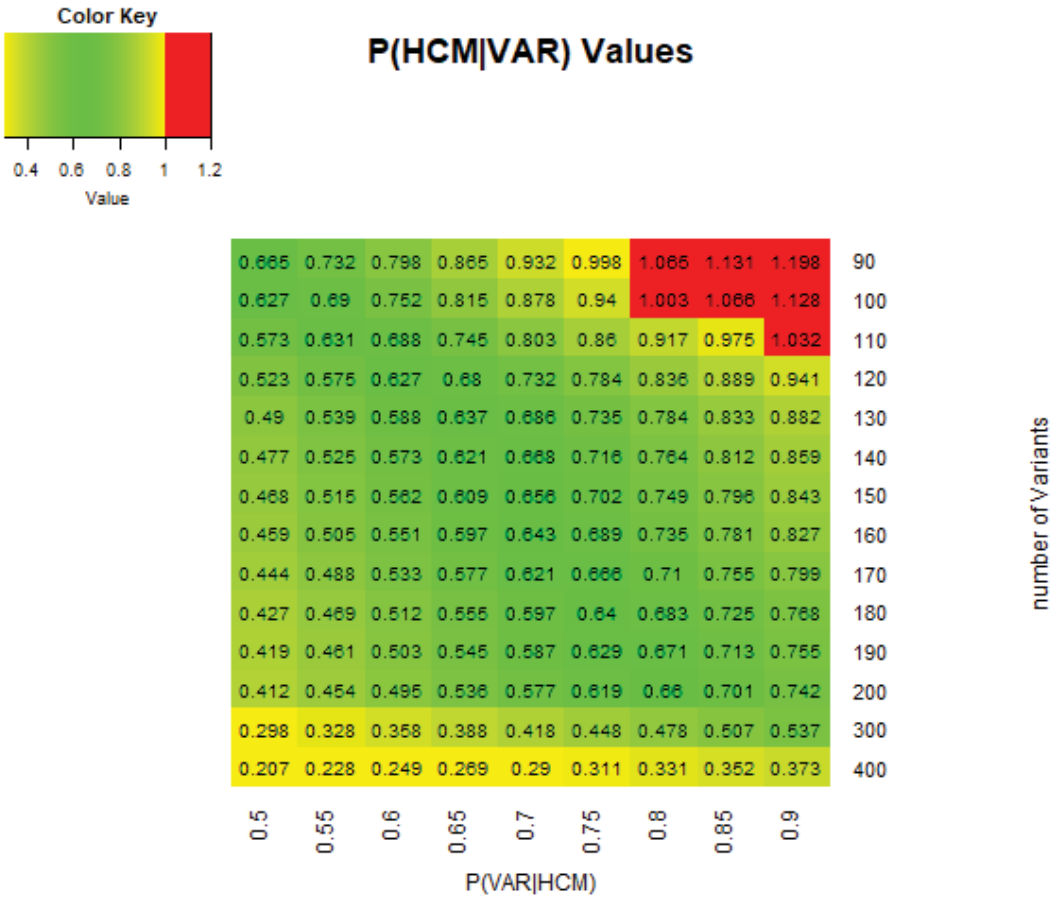
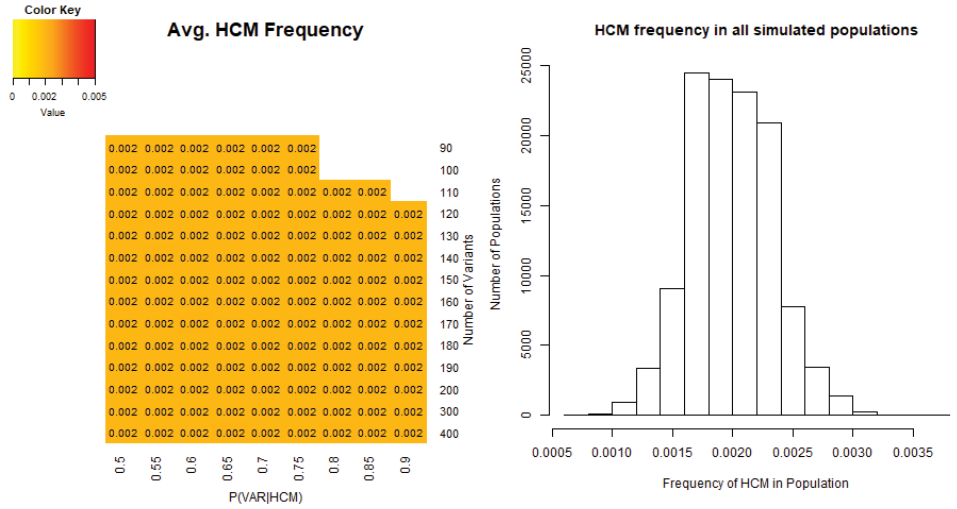


Figure 27: Varying of $P(HCM|VAR)$ (penetrance) with selected values of $P(VAR|HCM)$ and the $\#\ of\ variants$ used from the ranked variant list. Green indicates a more probable value, yellow less probable, and red an impossible value. Combinations of $\#\ of\ variants$ and $P(VAR|HCM)$ that return red penetrance values will not be run in this simulation. Note how the $P(HCM|VAR)$ increases with increasing values of $P(VAR|HCM)$ and decreases with increasing values of the $\#\ of\ variants$.

$P(HCM|VAR)$ and $P(HCM|VAR^C)$ will be used in the simulation. If an individual has a pathogenic variant, the chance they will have HCM is $P(HCM|VAR)$ for the given $P(VAR|HCM)$ and $\#\ of\ variants$, and the chance the will have HCM if they do not have a pathogenic variant is $P(HCM|VAR^C)$ for the given $P(VAR|HCM)$ and $\#\ of\ variants$. In all figures, the probabilities noted inside the arrows indicate how each subsequent group will be determined. Population representations in all figures are not to scale.

To demonstrate that this method effectively and accurately assigned individuals as having HCM in populations, the frequency of HCM was analyzed for the simulated populations created. The goal of the simulation is to have a relatively constant frequency of HCM to be 0.002, with values varying to a small extent between populations to account for random error. Figure 28a displays a heatmap of the average disease frequencies over 1000 simulated officer populations for each value of $P(VAR|HCM)$ and $\#\ of\ variants$, and figure 28b displays a histogram of the freqency of HCM for 119,000 simulated officer

populations, 1000 populations for each of the 119 $P(VAR|HCM)$ and $\#\ of\ variants$ combinations. The heatmap values are consistently seen to be averages of 0.002, and the histogram shows a distribution with 95% of the values between 0.0019992 and 0.0020046.



(a) Heatmap of Officer Simulation
$\sigma : \{0.00032, 0.00034, 0.00034, 0.00035, 0.00036\}$[1]

(b) Histogram of Officer Simulation
$\mu = 0.0020019, \sigma = 0.00047$

Figure 28: Distribution of frequency of HCM for the officer simulation. Generally accepted in literature to be 0.002 [3], this simulation produces the frequency of HCM at an accurate value with some variation.

8.1.4 Predicting Sudden Cardiac Death (SCD)

Sudden cardiac death (SCD) will be calculated using the probability that an individual has SCD given they have HCM, $P(SCD|HCM)$. This was found from literature to be on average 0.0081 per person per year [6, 38]. In this simulation, SCD will be calculated by taking an individual with HCM, and simulating the number of years they are in service. For each year, the chance they die of SCD is 0.0081. This is illustrated in Figure 29.

It is important to note that no accurate figure for the probability of SCD has been established for individuals who consistently exercise, as is common in the military. It is predicted that individuals who exercise regularly will have a higher incidence of SCD than those who do not, however, no data exist to determine how great the increase in risk is. Therefore, we will assume for this simulation that the rate of SCD due to HCM is the same as the general population.

Once all of the following simulations are complete, the questions listed in section 8.1 can be answered. A summary of all of the probabilities used in the simulation and how they were determined is located in Table 8.

[1]Standard deviations were taken for each of the 119 combinations of $P(VAR|HCM)$ and $\#\ of\ variants$ for the 1000 populations simulated for each combination. The standard deviations listed here, and below every heatmap, are given to represent an overview of the range of the standard deviations among the 119 combinations. The standard deviations for all heatmaps are listed as: minimum, 25th quantile, median, 75th quantile, maximum. A discussion on variation in these results is found in Section 11.

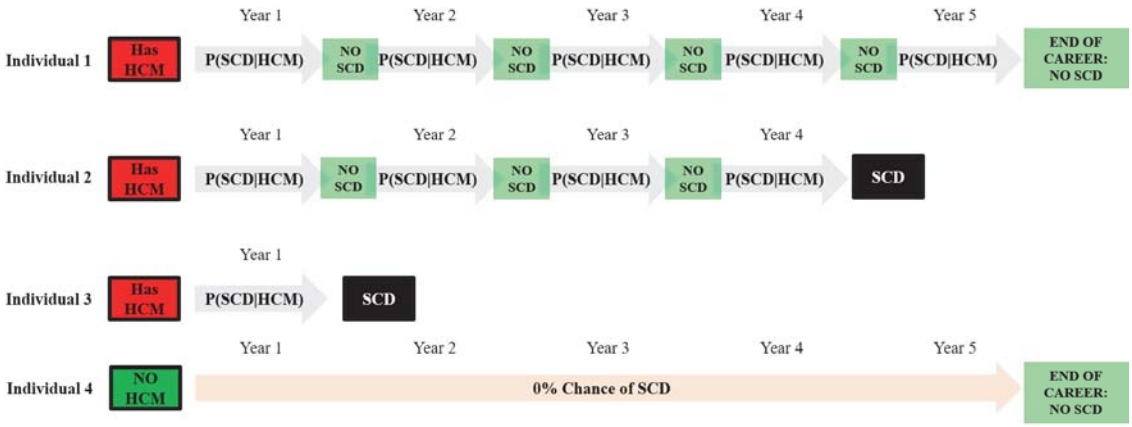


Figure 29: Sudden Cardiac Death (SCD) Simulation. Representing individuals who each serve for 5 years. Individual 1 has HCM, but makes it through all 5 years without SCD. Individuals 2 and 3 have SCD some point in their career. Individual 4 does not have HCM, and so has no chance of developing SCD in this simulation.

Table 8: Probability Values for Cost/Benefit Analysis

Probability	**Symbol**	**Value**
Probability of having disease in general population	$P(HCM)$	0.002
Probability of having a variant in general population	$P(VAR)$	Found from ranked variant list and frequencies of pathogenic variants in gnomAD
Probability of having a pathogenic variant given disease	$P(VAR\|HCM)$	Set to a range of values based on ranges found in literature (0.5-0.9)
Probability of having a variant given absence of disease	$P(VAR\|HCM^C)$	$\frac{P(VAR)-P(HCM)P(VAR\|HCM)}{1-P(HCM)}$
Probability of having disease given variant	$P(HCM\|VAR)$	$\frac{P(HCM)P(VAR\|HCM)}{P(VAR)}$
Probability of having disease given not having variant	$P(HCM\|VAR^C)$	$\frac{1-P(VAR\|HCM)}{1-P(VAR)}$
Probability of dying from sudden cardiac death per individual per year given having disease	$P(SCD\|HCM)$	0.0081 per year

8.2 Simulate Genetic Screening

Individuals that have a pathogenic variant according to the model cutoff will be identified by genetic screening. It is the genome, not the diseases status, that determines if an individual will be identified by genetic screening.

We assume in this simulation that if an individual has a pathogenic variant, genetic screening will be able to detect its occurrence. Next generation sequencing can call areas of greatest interest in genomes with an accuracy above 99.99% [39]. Because of this high accuracy of next generation sequencing and further development in accuracy, we assume that the it will be able to detect all pathogenic variants. Additionally, we do not desire to assign a particular accuracy or Q-score to a genetic test, because we do not desire to explicitly define the type of genetic test that is taking place in this simulation.

8.3 Simulate Echocardiogram Screening

As discussed in Section 7.2.1, echocardiograms are the typical tool for diagnosis of HCM. The image of the left ventricle given by an echocardiogram allows physicians to determine if the left ventricular walls are enlarged. However, there are different definitions for "enlarged" left ventricular walls, and the accuracy, sensitivity and specificity for each definition differs.

In this simulation, we test two definitions used by echocardiography, as defined by Rodday *et al.* First, a "max accuracy" setting that maximizes true positive rate and minimizes false positive rate (is at the upper left corner of the ROC curve as discussed in Section 7.6.3). A second definition, "max specificity" maximizes specificity (reduces false positives), while sensitivity decreases (false negatives increase). The values for sensitivity, specificity, false positive rate, and true positive rate are displayed in Table 9 [12].

Table 9: Probability Values for Echocardiogram [12]

Condition	Sensitivity	Specificity	False Positive Rate
Max Accuracy	0.851	0.851	0.149
Max Specificity	0.607	0.999	0.001

These values were used in the simulation to determine who receiving an echocardiogram test will be identified as having HCM or not having HCM. To do this, if an individual in the simulation had HCM (having HCM was determined through simulation in section 8.1), the chance they were classified as "having HCM" by the echocardiogram was the sensitivity, or true positive rate. If an individual *did not* have HCM, the chance they were classified as "*having* HCM" by the echocardiogram was the false positive rate (FPR). Figure 30 illustrates this determination.

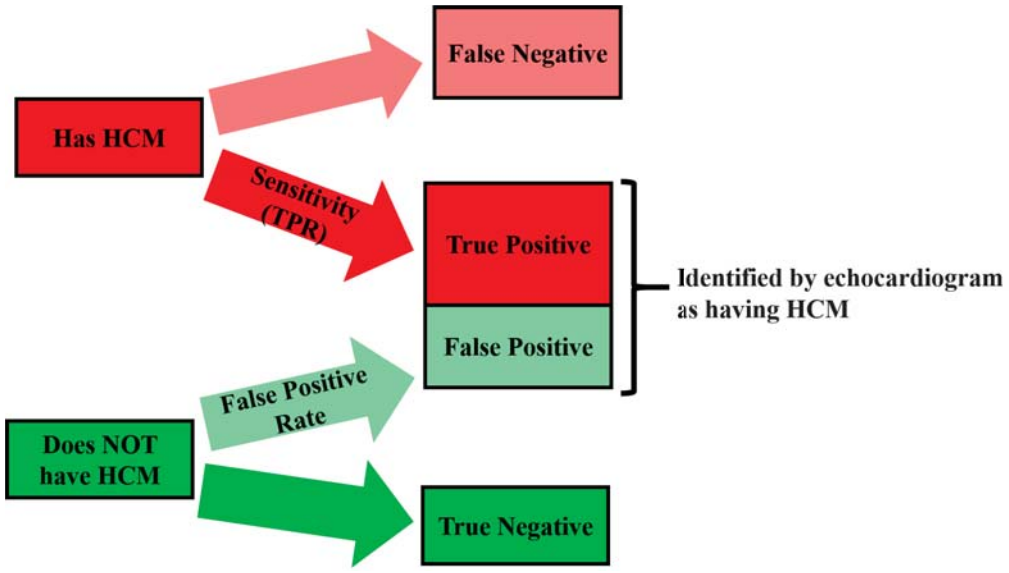


Figure 30: Echocardiogram screening simulation. Individuals were determined to have HCM in Section 8.1. If an individual had HCM, the TPR of the echocardiogram condition was used to determine the chance an individual was identified as having HCM. If an individual did NOT have HCM, the false positive rate was used as the chance an individivudal in this group was identified as "having HCM."

8.4 Costs

Since part of the goal of the cost/benefit analysis is to determine what screening option of the six cases in Table 7 would be best financially, the actual financial cost of the screening options must be taken into account, as well as the cost of *not* screening individuals. All cost measurements in this analysis are done using the United States dollar value in March of 2018.

Costs associated with sudden cardiac death include the benefit recuperation and cost associated with a death ("death cost") in the military in addition to the costs lost due to training an individual who is unable to perform their duties ("lost training cost"). Costs were split between officers and enlisted. The death cost remains the same between officers and enlisted, however the training cost for officers is significantly higher than for enlisted, due to the expensive training costs incurred from service academies, ROTC, OCS, flight training, and specialized community training. Expanded training costs were only found for Naval Officers. It is an assumed that Army and Air Force officers will have approximately the same training costs as Naval Officers. It is also important to note that depending on when an individual his died in their career, certain training costs may not be classified as "lost," as an individual may have utilized their training in a certain specialty before they die if they die later in their career. This is not taken into account in this simulation. An individual is considered to forfeit all of their training costs if a death during any time in the military is recorded. The reasoning behind this assertion is that only the initial training costs are included in this assessment (basic training, ROTC, and early specialized community training). Any additional training an individual undergoes later in their career is not accounted for. We are making the assumption that if an individual dies while on active duty, the military will forfeit training cost from some source,

Table 10: Costs Associated with Death in Military

Cost	Value	Reference
Death Cost	$100,000	[40]
Officer Training	$912,000	[41] Other brances offcier training cost assumed to be equal to Navy
Enlisted Training	$55,000	[42] Values include: direct training costs, training support, labor training, and recruitment and advertising costs. Values for officers are subtracted from total values to arrive at enlisted value.

which is included in this cost estimation. Table 10 lists the category of each cost associated with a death in the military, its value, and the reference used to determine the cost.

Costs associated with medical tests include the cost associated with genome sequencing and costs associated with an echocardiogram. Genome sequencing widely varies in cost, and is constantly changing in cost. Additionally, the United States Medicare program does not cover or maintain a price database for genetic sequencing. Because of this fact, the cost of genetic sequencing is varied in this cost/benefit analysis from $10-$1,000. Currently, an accurate estimate of the cost of whole-genome next generation genetic sequencing is approximately $1,000, and the cost of microarray genetic test analysis ranges from $30-$130 [28, 43]. However, this figure is rapidly changing due to technological improvements and depends on many factors including the equipment and the cost of the human labor associated with analysis. If the process of genomic screening is automated, the cost may be brought down significantly. The cost associated with an echocardiogram was found using data from FY 2015 as published in the Medicare cost database. Table 11 lists the category, value, and references of the cost of each medical procedure.

Table 11: Costs Associated with Medical Tests

Cost	Value	Reference
Genetic Test	$10-$1,000	[28, 43]
Echocardiogram	$2,506	Outpatient costs data, Medicare [27]. Used national average value billed by hospitals.

Each of these costs were used in the calculation of the total cost for each respective case. How the cost of each cases was calculated is illustrated in Table 12.

Table 12: Cost of Cases

P = total population size	
$p_{pos.\ genetic\ test}$ = population of individuals who have a positive genetic test	
d = number of individuals that die from SCD due to HCM (case dependent)	
C_{death} = cost of death gratuity	
$C_{training}$ = lost training cost	
$C_{genetic}$ = cost of genetic test	
C_{echo} = cost of echocardiogram	
Case 1	$d(C_{death} + C_{training})$
Cases 2 & 4	$d(C_{death} + C_{training}) + PC_{echo}$
Cases 3 & 5	$d(C_{death} + C_{training}) + PC_{genetic} + p_{pos.\ genetic\ test}C_{echo}$
Case 6	$d(C_{death} + C_{training}) + PC_{genetic}$

8.5 Population size and Years in Service

An accurate representation of the population size of the military should be utilized in this simulation. As stated previously, an enlisted population and an officer population will be simulated seperatley due to the different costs associated with the two. Additionally, the number of years in service and number of yearly accessions between the two groups differs.

The population size of the simulations tested represents the average number of military accessions for Fiscal years 2013, 2014 and 2015 [44]. Table 13 displays these values. These values will be used to create populations of individuals of the certain size.

The number of years in service for each group was found in a 2009 study on military force numbers [44], also listed in Table 7. These numbers will be used in calculating the number of individuals that die from sudden cardiac death. Figure 29 illustrates this calculation, where the simulation will simulate the average number of years that an individual is in the military, and for each year, there will be a $P(SCD|HCM) = 0.0081$ chance of dying from sudden cardiac death due to HCM while in the military [6].

Table 13: Force Strength Values Used in Analysis

Item	Value	Reference
Enlisted Accessions	152,054	[44] Average FY13,FY14,FY15
Officer Accessions	16,721	
Enlisted Average YOS	7 years	[7] Used 2009 value.
Officer Average YOS	11 years	

8.6 Simulation of Cases

Cases 1-6 are described in further detail below. It is important to note that, in each population simulation, the same genomes, HCM positive, HCM negative, and SCD due to HCM individuals were used for all cases. Each case simply reflects how individuals in each population were *detected* or how many predicted deaths were prevented. Each simulation was tested on the same set of 1000 populations with equal individuals possessing pathogenic variants, HCM, and predicted deaths.

Important to note is how individuals who are detected to have HCM are dealt with in this simulation. If an individual has been detected to have HCM by a screening test, they are discharged from the military before entry. We describe individuals with HCM that have been discharged due to these tests as "prevented" deaths because the individuals are given the opportunity to pursue treatment for their condition once the diagnosis is made, perhaps saving their lives.

8.6.1 Case 1: No Screening

In this case, the simulation will be run, and all individuals that are predicted to die from SCD due to HCM will do so without prevention. All individuals in the military will be retained, regardless of HCM or genetic status. Figure 31 illustrates how this case will be simulated.

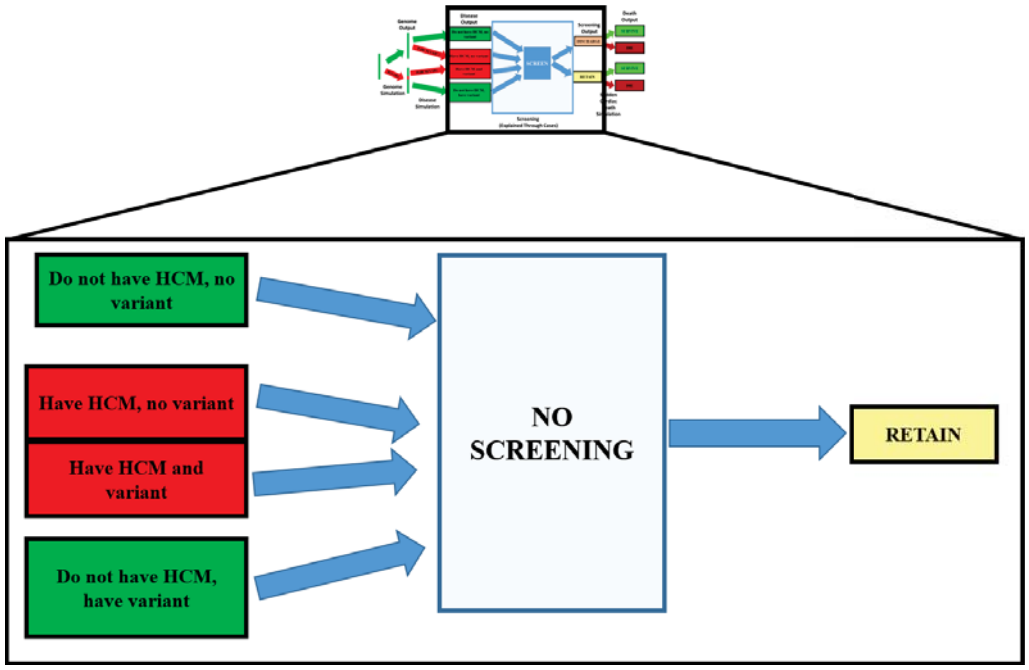


Figure 31: Case 1 will have no interventions in preventing death from SCD due to HCM. All individuals predicted to die from HCM in the simulation will do so.

8.6.2 Cases 2 and 4: Echocardiogram Only Tests

In each case, the simulation will be run, and individuals who are positive for an echocardiogram test will be discharged. All individuals who have HCM will have a chance of being detected equal to the sensitivity of the echocardiogram test, as outlined in Section 8.3 regardless of their genomic makeup. All individuals who *do not* have HCM will have a chance of being falsely discharged equal to the false positive rate of the echocardiogram test, as outlined in Section 8.3. This will generate two different populations of individuals that are discharged for each echocardiogram test.
Figure 32 illustrates how this screening is simulated.

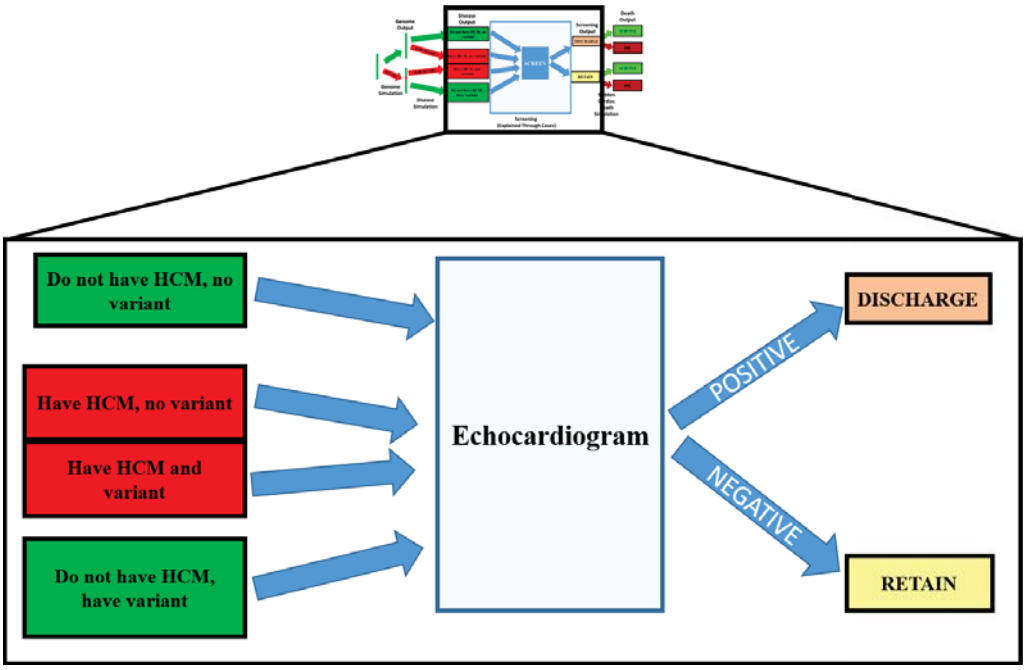


Figure 32: Cases 2 and 4 involve only echocardiogram tests. Shown here, the genetic makeup of an individual does not matter for screening. Section 8.3 describes how echocardiogram screening is simulated.

8.6.3 Cases 3 and 5: Genetic Screening Followed By Echocardiogram

In each case, the simulation will be run, and all individuals that have a pathogenic variant will undergo echocardiogram testing. Only individuals who are positive for both the echocardiogram *and* the genetic test will be discharged.

This echocardiogram testing, however, will have the same results as the echocardiogram testing that was done in cases 2 and 4 except that all cases with benign variants will not be discharged. All individuals who had a positive echo from Case 2 *and* have a pathogenic variant will be discharged in Case 3, and all individuals who had a positive echo from Case 4 *and* have a pathogenic variant will be discharged in Case 5. Figure 33 illustrates these cases.

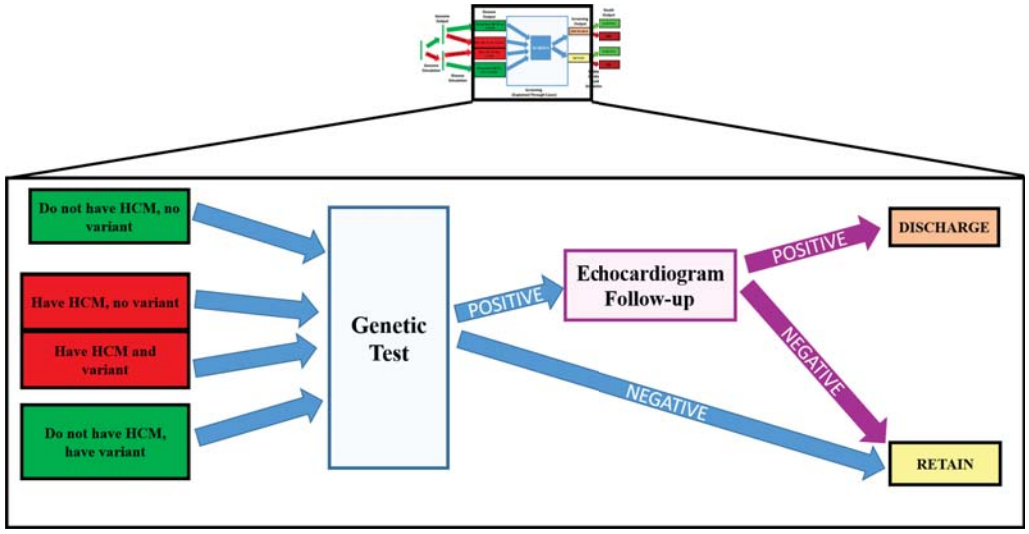


Figure 33: Cases 3 and 5 involve both genetic screening and a echocardiogram follow-up. This will be simulated by all individuals that have a pathogenic variant and had a positive echo from the respective "echocardiogram only" test will be discharged. Only individuals positive for both the echocardiogram and the genetic test will be discharged.

8.6.4 Case 6: Genetic Screening Only

In this case, only a genetic test will be simulated. All individuals who have a pathogenic variant in the simulation will be discharged, and all individuals who do not have a pathogenic variant will be retained. Individuals with the variant and disease will be true positives, individuals with the variant but not the disease will be false positives, individuals without the variant but with the disease will be false negatives, and individuals without the variant and without the disease will be true negatives. Figure 34 illustrates this case.

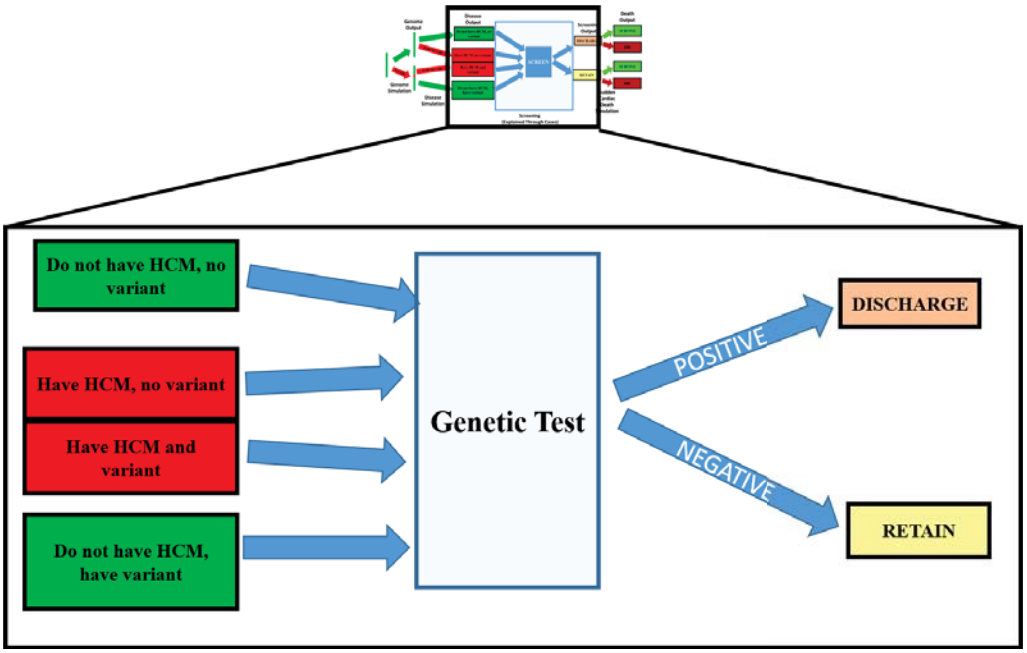


Figure 34: Case 6 involves only a genetic test.

9 Results of Cost/Benefit Analysis

Both enlisted and officer simulations were run for all six cases, with the 119 combinations of $P(VAR|HCM)$ and $\#\ of\ variatns$ as described in Section 7. We now look to interpret the results of these simulations.

Ultimately, this cost/benefit analysis looks to analyze:

1. How well do the cases detect HCM without classifying individuals who do not have HCM as diseased?
2. How well do the cases prevent Sudden Cardiac Death caused by HCM?
3. What is the overall monetary cost or benefit of each case?

Each of these items will be explored in depth. Ultimately, we look to conclude which cases perform the items enumerated above, and additionally conclude if some cases perform the items enumerated above better *only under certain* $P(VAR|HCM)$ and $\#\ of\ varaints$ values. We also look to compare how the cases performed differently between officer and enlisted simulations, and look to see what the results would be if the tests were used on a combined officer and enlisted population.

Data is displayed in the subsequent sections for each case and each condition as *averages* of the 1000 simulated populations that were created during this simulation. In other words, each value displayed in a heatmap is an average value over the course of 1000 simulated populations. We provide the standard deviations below every heatmap where appropriate, and discuss variation in the simulation in Section 11. We specifically use averages in this analysis because the military will be most interested in reducing costs, and the effect of the policies implemented, over the long run instead of being concerned about extrema.

9.1 Performance of Cases: Detecting HCM

How well the tests detect HCM was analyzed through a various set of measurements. These measurements work off of the principle of maximizing true positives and true negatives while minimizing false positives and false negatives. A contingency table, Table 14 explains what these values are.

Table 14: Contingency Table For HCM Detection

	Diseased	NOT Diseased
Discharged	True Positive	False Positive
Retained	False Negative	True Negative

The absolute values of these numbers can be found in Appendix C, where the trends and values for these absolute numbers are explored.

In addition to looking at raw numbers expressed in Table 14, we also look to use measurements that take the *relative values* of the conditions in the contingency table. These measurements are defined and outlined in Table 15.

Table 15: Measures to Assess Detection of HCM

Measure	Definition	Desired Value
Specificity	$\frac{True\ Negatives}{Total\ Negatives}$	1
Sensitivity	$\frac{True\ Positives}{Total\ Positives}$	1
False Discovery Rate	$\frac{False\ Positives}{False\ Positives+True\ Positives}$	0
False Omission Rate	$\frac{False\ Negatives}{FalseNegatives+True\ Negatives}$	0
Accuracy	$\frac{True\ Positives+True\ Negatives}{Total\ Population\ size}$	1

We look to analyze all of these measures in a methodical way. To do this, we outline here the process we will use to analyze each parameter.

1. Analyze the absolute values of these measures of the *officer* cases. Officer cases will be the first cases presented because of the greater cost of death an officer causes the military. These absolute values will be displayed in a heatmap for all cases, with each combination of $P(VAR|HCM)$ and $\#\ of\ varaints$. For all of the heatmaps, red indicates a higher value, and yellow indicates a lower value. From this table, we look to gather absolute numbers and descriptive concepts of trends in the data.

2. Display a graph where the measure being analyzed (for the officer case) is plotted against changing values of $\#\ of\ varaints$ at a fixed value of $P(VAR|HCM)$. This will demonstrate how the measure changes for each case with changing $\#\ of\ varaints$ while holding $P(VAR|HCM)$ constant.

3. Display a graph where the measure being analyzed (for the officer case) is plotted against changing values of $P(VAR|HCM)$ at a fixed value of $\#\ of\ varaints$. This will demonstrate how the measure changes for each case with changing $P(VAR|HCM)$ while holding $\#\ of\ varaints$ constant.

4. As described above, how one variable changes while holding the others constant for each case and for each measure will be found. However, it is possible that the variables may interact with each other, and how one variable affects the measure is dependent on the value of another. For example, a measure may increase and have a positive intercept for an increasing $\#\ of\ variants$ if the constant value of $P(VAR|HCM)$ is 0.7, but the same measure may decrease and have a negative intercept for an increasing $\#\ of\ variants$ if the $P(VAR|HCM)$ is held at 0.9. To determine whether this is occurring, we plotted the change in a measure for each case while changing one variable and holding the other constant, and then

changed the variable held constant *to a different value* and plotted the change for the measure for the variable again to see if any differences occurred. Additionally, value of $\frac{\partial measure}{\partial \#\ of\ varaints}$ was recorded for each constant value of $P(VAR|HCM)$ used in the simulation for each case, and the value of $\frac{\partial measure}{P(VAR|HCM)}$ was recorded for each value of $\#\ of\ varaints$ used in the simulation for each case. The meaning of these partial derivatives, and a more in-depth analysis of the interactions among variables is found in Appendix A.

Each of these items will be discussed relating it to the significance of the results. After the officer simulations are summarized, the same will be done for the enlisted simulations. However, if the enlisted simulations result in the same values as the officer simulations, figures will not be displayed in the text for the enlisted and combined simulations, and will be placed in Appendix B.

9.1.1 Accuracy

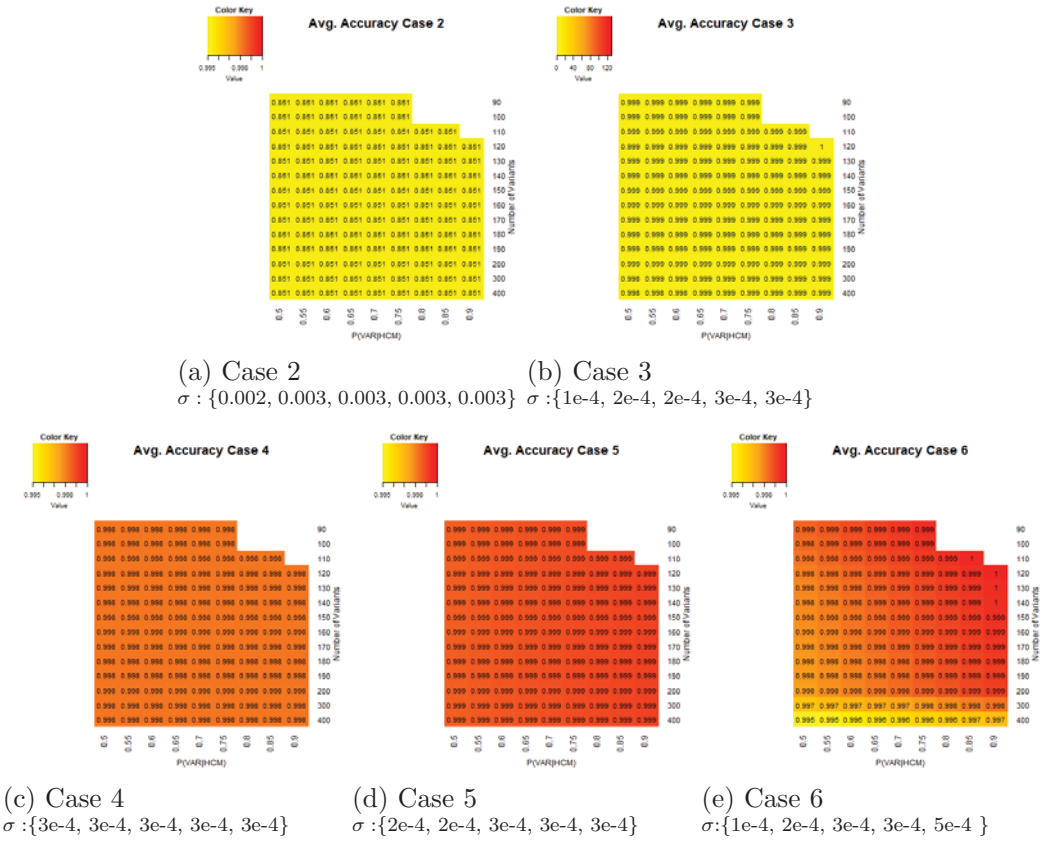
Accuracy is an overall measure that takes into account how well a test both identifies individuals who have disease and also identifies individuals who do not have disease. Its definition in our analysis is:

$$Accuracy = \frac{\#\ discharged\ and\ diseased\ +\ \#\ retained\ and\ NOT\ diseased}{total\ population} \tag{9}$$

We display in Figure 35 heatmaps for the average accuracy of the 1000 officer simulations for each $P(VAR|HCM)$ and $\#\ of\ varaints$ combination. In this figure, we can immediately see that cases 2 and 4 appear to have a constant accuracy measure, and cases 3 and 5 do not appear to fluctuate much at all. Case 6 does appear to fluctuate. We can also see from these heatmaps that Case 2 appears to have a much lower accuracy than the other cases. Cases 2 and 4 likely have unchanging accuracy numbers becasue they are not genetic tests, and so should not change with the genetic variables $P(VAR|HCM)$ and $\#\ of\ variants$.

In Figure 36, we display how accuracy changes with changing $\#\ of\ varaints$ with the constant $P(VAR|HCM)$ values of 0.5, 0.7 and 0.9 (chosen because they represent a range of the $P(VAR|HCM)$ values used in the study). We can see from these graphs that Case 5 does not appear to change with clanging $\#\ of\ varaints$ (has a slope of zero). We can also see that cases 3 and 6 have negative slopes, and so accuracy decreases with a greater $\#\ of\ varaints$. This is likely due to the fact that as the $\#\ of\ varaints$ increases with the same $P(VAR|HCM)$, the number of false positives will increase, as the number of individuals who have a pathogenic variant will increase while holding the number of individuals with both a variant and disease constant. Case 6 likely has the greatest slope because it is not checked by a secondary echocardiogram test. Case 5 likely has almost no slope because its secondary echocardiogram test is so specific, and will filter out nearly all of the false positives the genetic test does not. Additionally, the curves appear to shift upward for a larger $P(VAR|HCM)$ in every case.

Figure 37 displays how accuracy changes for a changing $P(VAR|HCM)$ with four constant values of $\#\ of\ variants$. It appears in all cases, the slopes are positive: that with



(a) Case 2
σ : {0.002, 0.003, 0.003, 0.003, 0.003}

(b) Case 3
σ :{1e-4, 2e-4, 2e-4, 3e-4, 3e-4}

(c) Case 4
σ :{3e-4, 3e-4, 3e-4, 3e-4, 3e-4}

(d) Case 5
σ :{2e-4, 2e-4, 3e-4, 3e-4, 3e-4}

(e) Case 6
σ:{1e-4, 2e-4, 3e-4, 3e-4, 5e-4 }

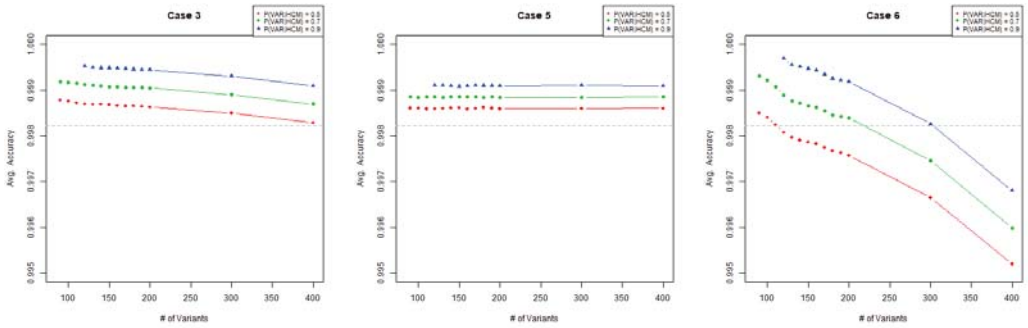
Figure 35: Heatmaps of the Accuracy for each officer case. Standard deviation summary given as $\sigma : \{min,\ 25^{th}\ quantile,\ median,\ 75^{th}\ quantile,\ maximum\}$

a greater $P(VAR|HCM)$, the tests will be more accurate. With changing the constant $\#\ of\ variants$, the curves appear to shift downward for an increasing $\#\ of\ variants$. This shift is more pronounced in Case 6, less pronounced in Case 3, and absent in Case 5, likely due to the selectivity of the echocardiogram tests used.

In Figures 36 and 37, the grey dotted line represents the average accuracy of Case 4. Cases 3 and 5 appear to have higher accuracy than Case 4 for all $P(VAR|HCM)$ and $\#\ of\ variants$ combinations. Case 6 surpasses Case 4 only for low $\#\ of\ variants$ and high $P(VAR|HCM)$ combinations.

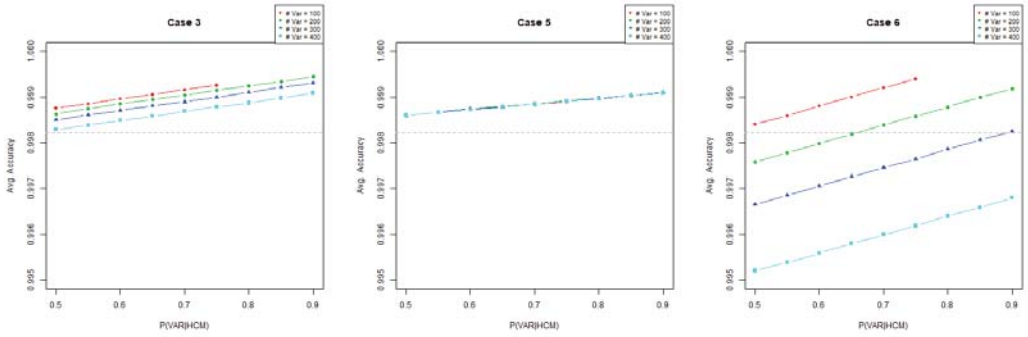
Accuracy of enlisted and officer populations was found to be similar. Graphs for the enlisted simulations can be found in Appendix B.

It is important to note that accuracy, as a measure to find the overall best screening method, is an incomplete measure. In combining both how well the test detects HCM and how well the test does not overclassify HCM, we lose the ability to distinguish what exactly is happening to each model: whether the model overclassifes too many individuals as diseased or does not classify enough. Additionally, it can be seen that the accuracies of these measurements are all quite high. This is because, in part, HCM is a disease that occurs in 1 in 500 individuals in the population. If a test simply never detected HCM for anyone, its accuracy would be above 0.99. Therefore, small changes in accuracy are



(a) Case 3 (b) Case 5 (c) Case 6

Figure 36: Accuracy, where the $\#\ of\ variants$ values were changed for three different $P(VAR|HCM)$ constants. Notice the negative slope for Cases 3 and 6, with nearly flat lines for Case 5. The grey line indicates the average Accuracy of Case 4.



(a) Case 3 (b) Case 5 (c) Case 6

Figure 37: Accuracy, where the $P(VAR|HCM)$ values were changed for four different different $\#\ of\ variants$ constants. Notice the positive slope for all cases, and how the curves shift up for a larger $P(VAR|HCM)$. The grey line indicates the average Accuracy of Case 4.

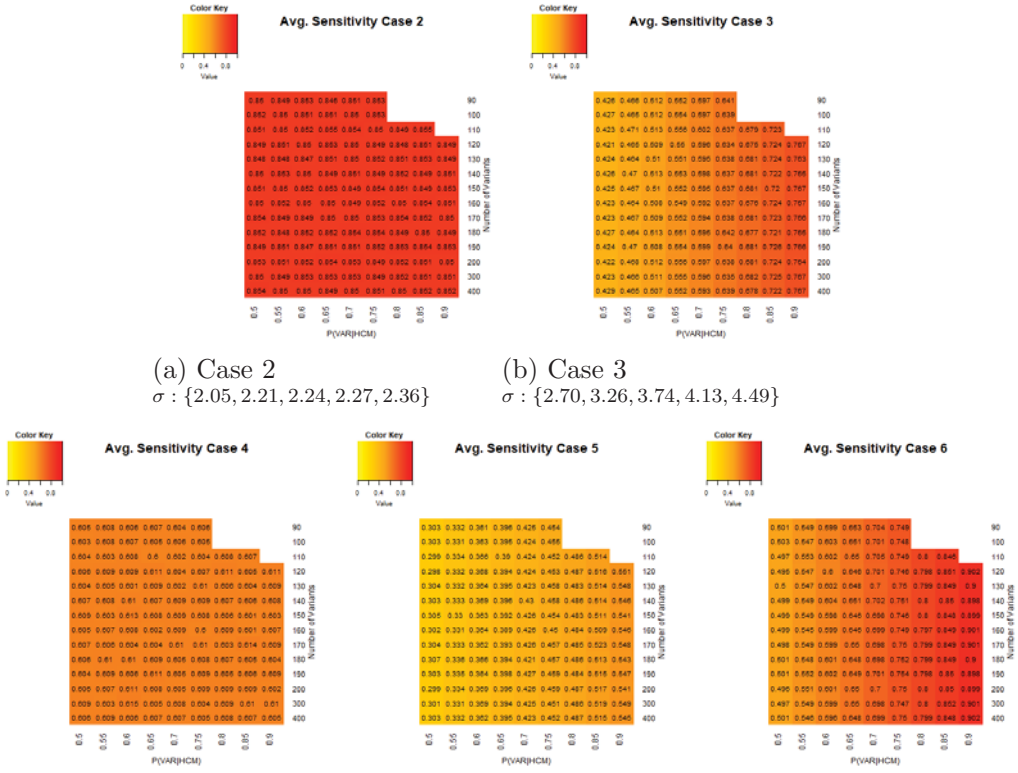
more important, and it is important to distinguish why each of these test possess the accuracy measures they do. This will be done in the forthcoming analysis of other measures.

9.1.2 Sensitivity

The sensitivity measures how well a test is able to identify individuals who are truly positive, or in this case, have HCM. For this simulation, it is defined according to Equation 10.

$$Sensitivity = \frac{\#\ of\ people\ discharged\ and\ diseased}{\#\ of\ people\ diseased} \tag{10}$$

A larger sensitivity indicates that more individuals who were diseased were identified as such. Figure 38 displays heatmaps of the average sensitivity over the 1000 officer simulations for each case in which screening occurred for every $P(VAR|HCM)$ and $\#\ of\ varaints$ combination.



(a) Case 2
σ : {2.05, 2.21, 2.24, 2.27, 2.36}

(b) Case 3
σ : {2.70, 3.26, 3.74, 4.13, 4.49}

(c) Case 4
σ : {3.41, 3.54, 3.60, 3.65, 3.77}

(d) Case 5
σ : {3.78, 4.16, 4.40, 4.63, 5.02}

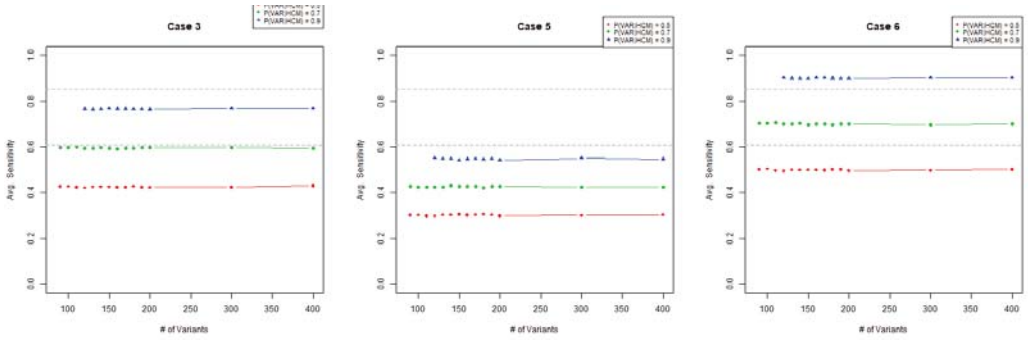
(e) Case 6
σ : {1.76, 2.60, 3.25, 3.71, 4.19}

Figure 38: Heatmaps of the sensitivity for each officer case. Standard deviation summary given as $\sigma : \{min,\ 25^{th}\ quantile,\ median,\ 75^{th}\ quantile,\ maximum\}$

We first explore Figure 38. From initial analysis of the heatmaps, it can be seen that for cases 2 and 4, little to no variation exists in the sensitivity for changing $P(VAR|HCM)$ or $\#\ of\ variants$. This is expected, as Cases 2 and 4 do not include any genetic screening, and so are not affected by the variance in genetic values. Case 2 appears to have a consistent value of approximatley 0.85, and Case 4 appears to have a constant approximate value of 0.61. However, for cases 3, 5 and 6, the sensitivity appears to vary for different

values of $P(VAR|HCM)$ and $\#\ of\ variants$.

In Figure 39, the average sensitivity for each genetic case (Case 3, 5 and 6) is plotted against a changing number of variants for three different constant $P(VAR|HCM)$ values of 0.5, 0.7 and 0.9. These three different values were chosen because they represent a range of the entire $P(VAR|HCM)$ values used in this simulation (from 0.5 to 0.9). For all three cases, the slope of all lines appear to be zero. However, the y-intercepts of the lines appear to differ. For a greater $P(VAR|HCM)$, the y-intercept also increase. For example, in Case 3, a $P(VAR|HCM) = 0.5$ yields a consistent sensitivity value for all $\#\ of\ variants$ of approximately 0.4. However, when $P(VAR|HCM) = 0.5$, Case 3 has a consistent sensitivity value for all $\#\ of\ variants$ of approximately 0.75. This increase in y-intercept and constant 0 slope is noted for all cases. Additionally, the y-intercepts from case to case for the same $P(VAR|HCM)$ constant value appear to differ as well. Case 5 appears to have the lowest sensitivity values, while Case 6 appears to have the highest. This is likely due to the fact that Case 6 is not "checked" by a follow-up echocardiogram. A follow-up echocardiogram will have a certain false negative rate, and thus will sometimes classify individuals who are actually diseased as "not diseased." This causes the sensitivity to decrease. Case 3 decreases less than Case 5 most likely because its echocardiogram is more sensitive to HCM than the echocardiogram used in Case 5 is.

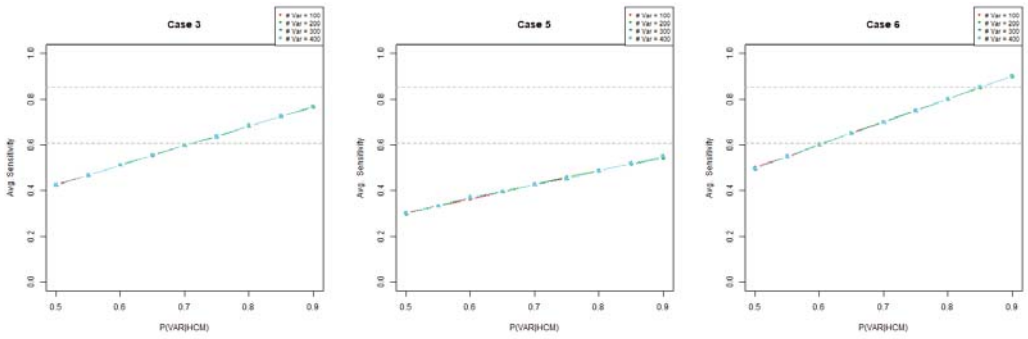


(a) Case 3 (b) Case 5 (c) Case 6

Figure 39: Sensitivity, where the $\#\ of\ variants$ were changed for three different constant values of $P(VAR|HCM)$. Notice that the slope of each line is approximately zero, with the y-intercepts of the lines increasing as the constant value for $P(VAR|HCM)$ increases. Also note how Case 6 has the highest absolute values for sensitivity for any given $P(VAR|HCM)$, and Case 5 has the lowest. The lower grey line at approximately 0.6 indicates the average sensitivity of Case 4, and the upper grey line at a value of approximately 0.85 indicates the average sensitivity for Case 2.

In Figure 40, the average sensitivity for each genetic case is plotted against a changing $P(VAR|HCM)$ for four different constant $\#\ of\ variants$ values of 100, 200, 300, and 400. These three different values were chosen because they represent a range of the entire $\#\ of\ variants$ values used in this simulation (from 100 to 400). For all three cases, each constant value of $\#\ of\ variants$ appeared to give the same exact line for each case. For each case, the slope of the lines appeared to be positive and constant. However, the slope of the lines for Case 6 appear to be the greatest, followed by Case 3 and then Case 5. The y-intercepts for Case 6 also appear to be the greatest, followed by Case 3 and then

Case 5. The reason for this difference between cases is likely due to the fact that cases 3 and 5 are checked by echocardiograms as mentioned above. We see, overall, that the sensitivity increases with increasing $P(VAR|HCM)$.



(a) Case 3 (b) Case 5 (c) Case 6

Figure 40: Sensitivity, where the $P(VAR|HCM)$ values were changed for four different $\#\ of\ variants$ constants. Lines did not change whatsoever for different $\#\ of\ variants$ constants. Notice the positive slope for all three cases. Note how the slope and y-intercept increases from Case 5 to 3 to 6. The lower grey line at approximately 0.6 indicates the average sensitivity of Case 4, and the upper grey line at a value of approximately 0.85 indicates the average sensitivity for Case 2.

Also of note is when certain values for the sensitivity for the genetic cases surpass the echocardiogram cases (approximately 0.85 for Case 2 and 0.61 for Case 4. The average sensitivities for these two cases are plotted as dotted grey lines in Figures 39 and 40). Case 3 appears to surpass the Case 4 value at approximately when a $P(VAR|HCM) = 0.7$ or greater is given. Case 6 appears to surpass the Case 4 value with a $P(VAR|HCM) = 0.6$, and appears to surpass the sensitivity of Case 2 with a $P(VAR|HCM) = 0.85$. Cases 3 and 5 do not surpass the sensitivities of their respective echocardiogram tests that are used in the cases to "check" the genetic test. This is because, with the genetic test, a certain number of diseased individuals do not have a variant, and so will not be identified by the genetic test. When the echocardiogram is used to "check" the genetic test, the sensitivity will decrease further.

Additionally, the sensitivity analysis was carried out on the enlisted simulations. However, the enlisted simulations returned approximately the same values as the officer simulations for a given $P(VAR|HCM)$ and $\#\ of\ varaints$ combination. Unlike for absolute measures of TP, FN, FP, and TN, the sensitivity is a relative measure, and so does not increase with an increased population. Graphs illustrating the sensitivity for the enlisted simulation can be found in Appendix A.2.

9.1.3 Specificity and False Positive Rate

Specificity measures how well a test can distinguish if people do *not* have a disease. It is defined in this simulation as:

$$Specificity = \frac{\#\ of\ people\ retained\ and\ NOT\ diseased}{\#\ of\ people\ NOT\ diseased} \tag{11}$$

False positive rate (FPR) measures how often a test calls an individual that is not diseased as diseased. It is defined in this simulation as:

$$FPR = \frac{\#\ of\ people\ discharged\ and\ NOT\ diseased}{\#\ of\ people\ NOT\ diseased} \tag{12}$$

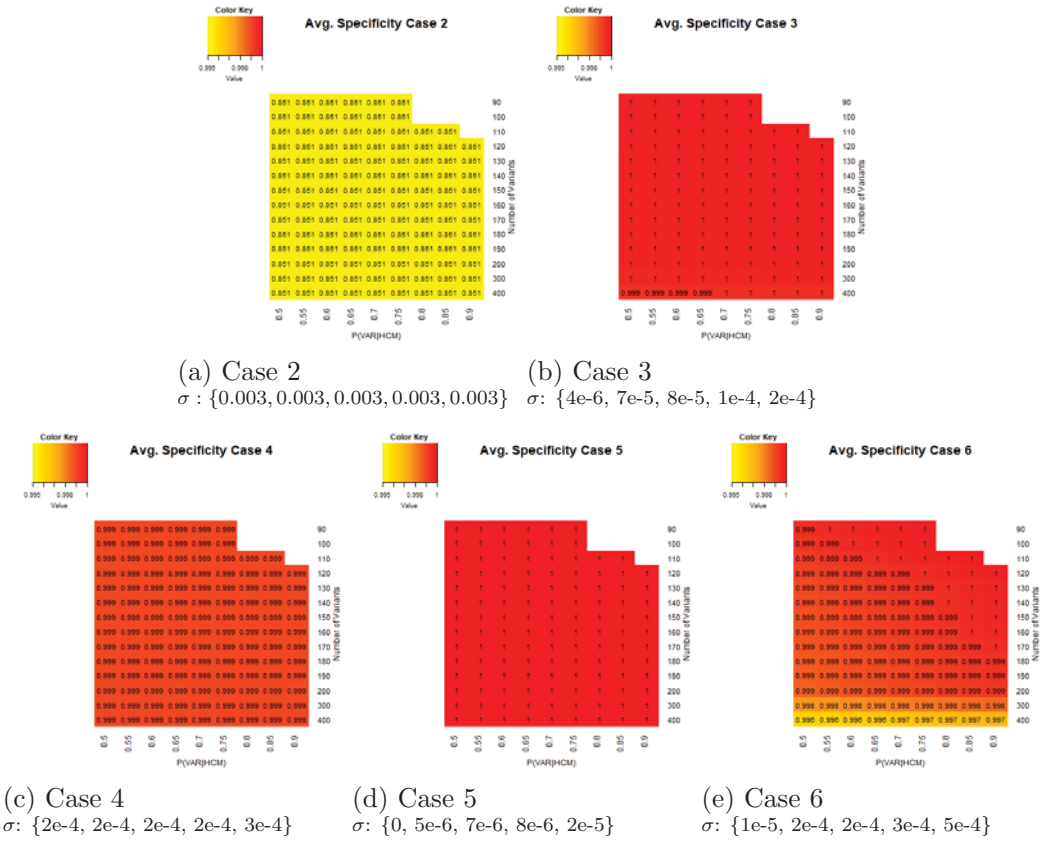
Additionally, FPR and Specificity are related to each other by:

$$FPR = 1 - Specificity \tag{13}$$

Because of the relationship described in Equation 13, as specificity increases, FPR will decrease. Thus, a model with the highest specificity will also have the lowest FPR. We will not report FPR in this report, and instead assume the reader understands that with a higher specificity, FPR will be less. Also of note is that these, like sensitivity, are relative and not absolute terms. Thus, the absolute number of false positives does not guarantee a specific specificity without knowledge of the population size and number of individuals not diseased.

Figure 41 displays heatmaps of the average value of the specificity for all officer cases over the 1000 simulations for every $P(VAR|HCM)$ and $\#\ of\ variants$ combination. Exploring this figure, we see that Case 2, Case 4 and Case 5 do not appear to vary for any values of $P(VAR|HCM)$ or $\#\ of\ variants$. This makes sense for the non-genetic cases 2 and 4, since they are not expected to vary for genetic parameters. However, Case 5 involves a genetic test, and would be expected to vary for changing genetic parameters. A likely reason we see no variation for Case 5 is the fact that the genetic test is followed up by an echocardiogram at maximum specificity, and for that reason, very few, if any, false positives will result after the echocardiogram test. This very specific sequence of tests and very through "check" on the genetic test likely allows Case 5 to have a very high specificity that does not vary much with changing genetic values. Also noted from the heatmaps is the much lower specificity for Case 2 (0.851) than for any of the other cases (0.996 and higher). This is likely due to the large false positive rate of the Case 2 echocardiogram classifying many individuals "diseased" that are actually not diseased.

Figure 42 displays how the specificity changes with a changing $\#\ of\ variants$ while holding $P(VAR|HCM)$ constant. Just as for sensitivity, we display here this change for three different constant values of $P(VAR|HCM)$ of 0.5, 0.7 and 0.9. Through Figure 42, it can be seen that the specificity decreases with an increased $\#\ of\ variants$ for cases 3 and 6.



(a) Case 2
$\sigma : \{0.003, 0.003, 0.003, 0.003, 0.003\}$

(b) Case 3
σ: {4e-6, 7e-5, 8e-5, 1e-4, 2e-4}

(c) Case 4
σ: {2e-4, 2e-4, 2e-4, 2e-4, 3e-4}

(d) Case 5
σ: {0, 5e-6, 7e-6, 8e-6, 2e-5}

(e) Case 6
σ: {1e-5, 2e-4, 2e-4, 3e-4, 5e-4}

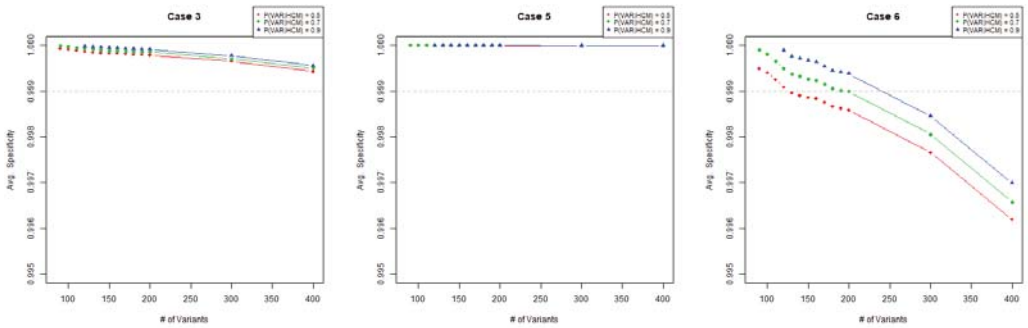
Figure 41: Heatmaps of the specificity each Officer case. Case 2 has a much larger Specificity value than any of the other cases. Standard deviation summary given as $\sigma : \{min,\ 25^{th}\ quantile,\ median,\ 75^{th}\ quantile,\ maximum\}$

This is likely due to the fact that as the $\#\ of\ variants$ are increased, the number of individuals that would be classified by a genetic test as "diseased" also increases, however, the actual number of individuals that have a variant and have disease remain the same for the same $P(VAR|HCM)$. Because of this, a genetic test for a larger $\#\ of\ variants$ and the same $P(VAR|HCM)$ will call more individuals as diseased when the same number of individuals are actually diseased, increasing the number of false positives, and thus decreasing the specificity. When a different $P(VAR|HCM)$ constant value is used, the slopes of the specificity curves appear to remain the same, however the y-intercepts appear to rise for increasing $P(VAR|HCM)$. This is likely because as $P(VAR|HCM)$ increases, more individuals that have a variant will have disease, decreasing the number of false positives for a genetic test. Also noted in this figure is the much larger slope for Case 6 than for Case 3. This is likely due to the echocardiogram follow-up in Case 3 causing the genetic effects to decrease. For Case 5, the effects of the genetic parameters are virtually zero with such a selective echocardiogram (slope of Case 5 is zero).

Figure 43 displays the specificity variation with changing $P(VAR|HCM)$ given four constant $\#\ of\ variant$ values of 100, 200, 300 and 400. From Figure 43, it can be seen that cases 3 and 6 both increase in specificity with an increase in $P(VAR|HCM)$. Additionally, the y-intercepts of cases 3 and 6 increase with increasing $P(VAR|HCM)$. The same pattern exists where Case 6 has a higher slope and more variation in slope intercepts

than Case 3, and Case 5 sees no variation for change in $P(VAR|HCM)$.

It is important to note, however, that although Case 6 seems to vary more with $P(VAR|HCM)$ and $\#\ of\ variants$ than cases 5 and 3, it does not mean that Case 6 has a higher specificity than cases 5 and 3. Case 5 has consistently a specificity of approximately 1, which is the ideal value for specificity. Case 3 has consistently higher values of specificity than Case 6. These results are due to the selective nature of the "checks" on genetic screening that the additional echocardiograms allow for cases 3 and 5. Comparing cases 3, 5 and 6 to cases 2 and 4, it can be immediately seen from the heatmaps that cases 3, 5 and 6 always have significantly higher specificites than Case 2. Cases 3 and 5 also have consistently higher values of specificity than Case 4, which is displayed as the grey dotted line on Figures 42 and 43. Case 6, however, only surpasses Case 4 in specificity for certain lower values of $\#\ of\ variants$ and higher values of $P(VAR|HCM)$.

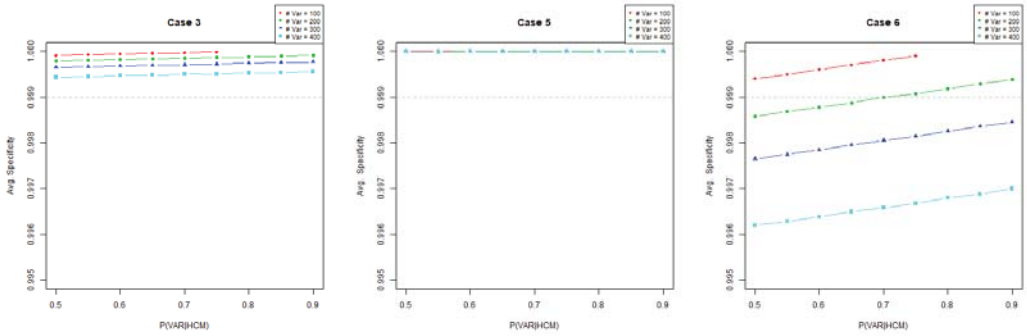


(a) Case 3 (b) Case 5 (c) Case 6

Figure 42: Specificity, where the $\#\ of\ variants$ were changed for three different constant values of $P(VAR|HCM)$. Notice that the slopes of the lines for Case 6 are the most negative, and the slopes of the lines for Case 3 have smaller magnitudes, while Case 5 has flat lines. Increasing $P(VAR|HCM)$ shifts the curves up. Dotted grey line is the average value of specificity for Case 4.

It is also important to note why such small changes in specificity (from 1.000 to 0.998) are noted as important. Specificity gives a the fraction of correctly classified individuals relative to the fraction of *non-diseased* individuals in the population. Thus, a test with a 90% specificity rate would misclassify 1,000 individuals if the non-diseased population is 10,000. In the case of HCM in officers or enlisted in this simulation, the healthy non-diseased population of individuals is well over 10,000 individuals. Because of this, a small change in specificity can affect tens, or even hundreds of individuals. It would be unacceptable for a diagnostic test to misclassify thousands of individuals as diseased when they were not diseased, and so looking for trends between a specificity of 0.997 and 0.999 is important because the changes will affect many individuals.

In Appendix B.3, results for the average Specificity among the 1000 enlisted simulations are displayed. These values exhibit not only the same trends as the officer simulations, but have approximately the same *values* as the officer simulations due to the relative nature of the measure.



(a) Case 3 (b) Case 5 (c) Case 6

Figure 43: Specificity, where the $P(VAR|HCM)$ was changed for four different constant values of $\#\ of\ variants$. Cases 3 and 6 have positive slopes, with Case 6 having a greater slope and more variation in intercepts for different values of $\#\ of\ variants$. Case 5 has flat lines at approximately 1. The dotted grey line represents the average value for the specificity of Case 4.

9.1.4 False Discovery Rate

Sensitivity and specificity both rely on values of how well a screening test performs with regard to all of the individuals who are diseased or all of the individuals who are not diseased. However, the False Discovery Rate (FDR) looks to assess how well a screening test performs *in relation to the population that it classifies as diseased*. The False Discovery Rate is defined for this situation as:

$$FDR = \frac{\#\ of\ individuals\ discharged\ and\ NOT\ diseased}{\#\ of\ individuals\ discharged} \tag{14}$$

The false discovery rate is also $1 - Posivie\ Predictive\ Value\ (PPV)$, which is defined as:

$$PPV = \frac{\#\ of\ individuals\ discharged\ and\ diseased}{\#\ of\ individuals\ discharged} \tag{15}$$

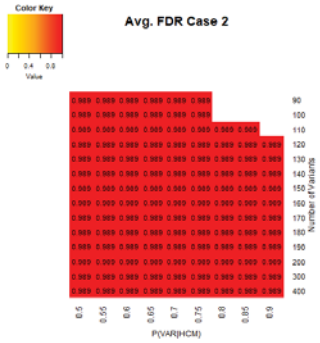
We will report in this analysis only the FDR, however the PPV can be determined from the reported FDR. The lower the FDR, the greater the chance that an individual that is reported as "diseased" by the screening test will actually be diseased.

The average FDR for each of the 1000 officer simulations for each $P(VAR|HCM)$ and $\#\ of\ variants$ combination is reported in Figure 44. From this figure, we can see the pattern that has occurred previously: cases 2 and 4 do not vary with changing genetic parameters, whereas cases 3, 5 and 6 appear to vary. Case 2 also appears to have a much higher FDR value than the other cases (approximately 0.99).

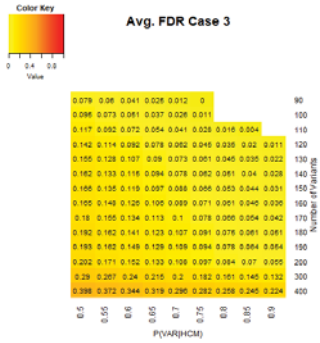
Figure 45 displays how FDR varies with $\#\ of\ varaints$ with constant values of $P(VAR|HCM)$ of 0.5, 0.7 and 0.9. From these figures, it can be seen that both cases 3 and 6 appear to increase in FDR with an increasing $\#\ of\ varaints$. However, Case 6 appears to have a greater overall slope than Case 3. Additionally, unlike sensitivity and specificity, the increase in FDR does not necessarily look to be linear, especially for Case 6. Instead, it appears to follow a more logistical function pattern, with a decreasing slope as the $\#\ of\ variants$ increase. Case 5 appears to increase only marginally as the $\#\ of\ variants$ increases. For a greater $P(VAR|HCM)$, the slopes for cases 3 and 6 appear to remain the same, with the curves shifted up.

In Figure 46, the change in FDR with changing $P(VAR|HCM)$ is plotted. In these graphs, for cases 3 and 6, the slopes appear to be negative: with increasing $P(VAR|HCM)$ and constant $\#\ of\ variants$, FDR decreases. This is likely due to the fact that if more individuals with variants have HCM, there will be less false positives in a genetic test. Case 6 appears to have the most negative slope, as well as the greatest y-intercepts, which Case 3 having smaller slopes and y-intercepts. Case 5 appears to have a marginal, if no slope likely due to the large corrective effect of the specific echocardiogram.

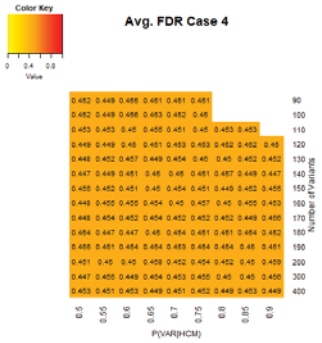
Also displayed in Figures 45 and 46 are two grey dotted lines. The lower grey lines represents the average FDR for all $P(VAR|HCM)$ and $\#\ of\ variants$ combinations for Case



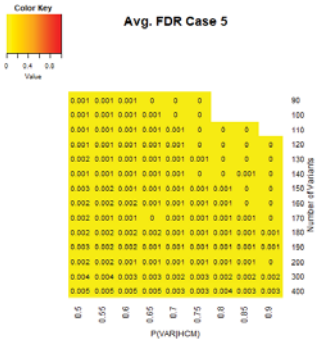
(a) Case 2
σ: {0.002, 0.002, 0.002, 0.002, 0.002}



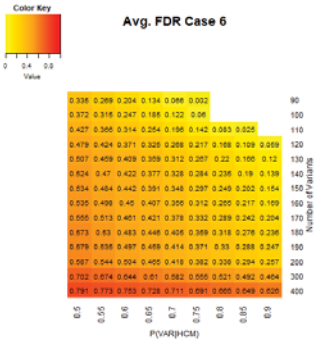
(b) Case 3
σ: {0.003, 0.005, 0.006, 0.008, 0.1}



(c) Case 4
σ: {0.08, 0.08, 0.08, 0.08, 0.09 }



(d) Case 5
σ: {0, 0.006, 0.009, 0.012, 0.026}

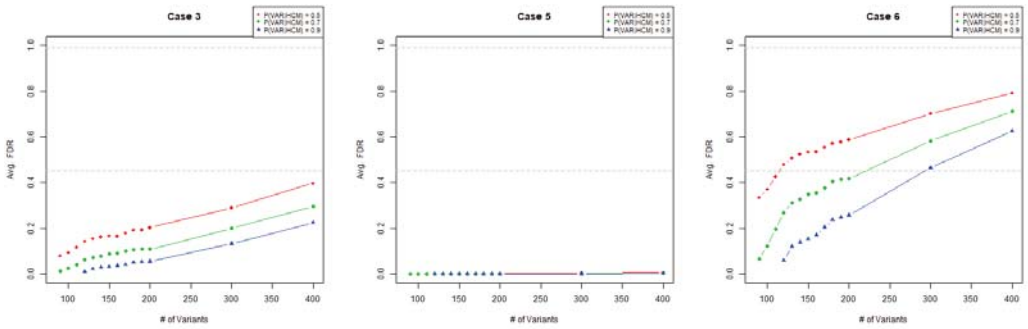


(e) Case 6
σ: {0.009, 0.067, 0.077, 0.083, 0.098}

Figure 44: Heatmaps of the average FDR for each Officer case.
Standard deviation summary given as: σ: {min, 25th quantile, median, 75th quantile, maximum}.

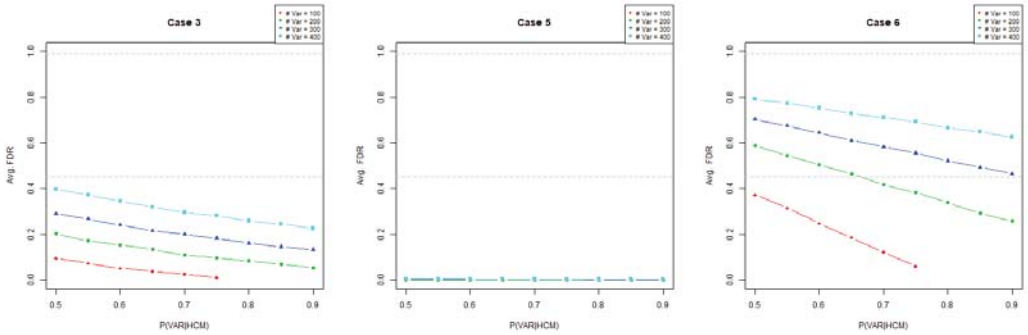
4. The upper grey dotted lines represent the average FDR for Case 2. It can be seen that for all values displayed by the genetic tests in the figures, never does a genetic test surpass the FDR of Case 2. Additionally, Cases 3 and 5 never surpasses the FDR for Case 4. Case 6, for some large $\#\ of\ variants$ values and small $P(VAR|HCM)$ values, surpasses the FDR for Case 4. Cases 3 and 5 likely have low FDRs due to the multi-step screening process that they must undergo. Case 6 does not have that multi-step screening process. It is important to note, however, that overall, for any $P(VAR|HCM)$ and $\#\ of\ variants$ combinations tested, cases 3 and 5 perform better with regard to FDR than the pure echocardiogram cases 2 and 4.

In Figure S17, values for the average FDR among the 1000 enlisted simulations are displayed for each $P(VAR|HCM)$ and $\#\ of\ varaints$ combination. These values exhibit not only the same trends as the officer simulations, but have approximately the same *values* as the officer simulations due to the relative nature of the measure.



(a) Case 3 (b) Case 5 (c) Case 6

Figure 45: FDR, where the *# of variants* were changed for three different constant values of $P(VAR|HCM)$. Notice that the slopes of the lines for Case 6 are the most positive, and the slopes of the lines for Case 3 have smaller magnitudes, while Case 5 has nearly flat lines. Increasing $P(VAR|HCM)$ shifts the curves up. Also note the somewhat logistical behavior of the Case 6 line. Lower Dotted grey line is the average value of FDR for Case 4, upper dotted grey line is the average value of FDR for Case 2.



(a) Case 3 (b) Case 5 (c) Case 6

Figure 46: FDR, where the $P(VAR|HCM)$ was changed for four different constant values of *# of variants*. Cases 3 and 6 have negative slopes, with Case 6 having a greater slope and more variation in intercepts for different values of *# of variants*. Case 5 has flat lines at approximately 0. The lower dotted grey line represents the average value for the FDR of Case 4, the upper dotted grey line represents the average value for the FDR of Case 2.

9.1.5 False Omission Rate

Just as false discovery rate measures the rate that individuals are falsely classified when discharged, false omission rate (FOR) measures the rate that individuals are falsely classified when retained. It is defined as:

$$FOR = \frac{\#\ of\ individuals\ diseased\ and\ retained}{\#\ of\ individuals\ retained} \tag{16}$$

Negative predictive value is an indication of how likely, if a test is negative, that the individual classified as "not diseased" is actually not diseased. It is defined as:

$$NPV = \frac{\#\ of\ individuals\ NOT\ diseaed\ and\ retained}{\#\ of\ individuals\ retaiend} \tag{17}$$

Just as PPV is $1 - FDR$, NPV is also defined as:

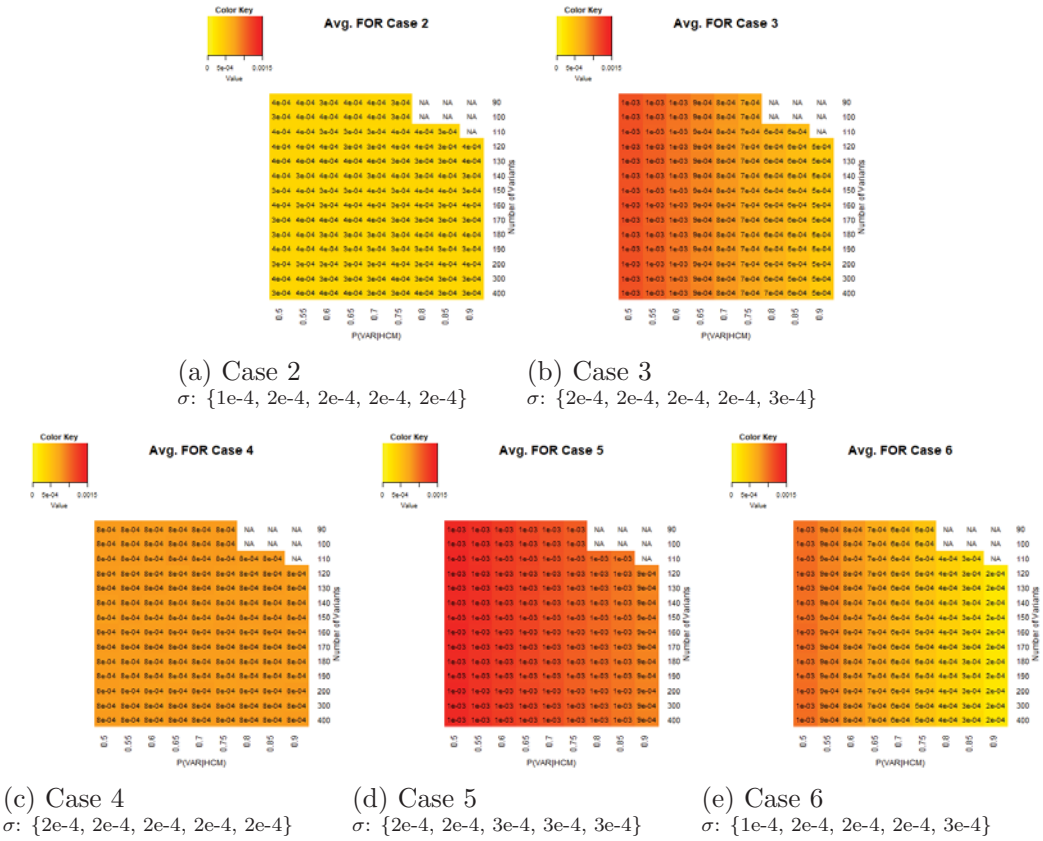
$$NPV = 1 - FOR \tag{18}$$

Due to the above relationship, we will not explicitly define NPV, but it can be found through the FOR, which we will explicitly analyze. A large FOR corresponds to a small NPV, and vice versa.

In Figure 47, displayed is the average false omission rate among the 1000 officer simulations for every combination of $P(VAR|HCM)$ and $\#\ of\ variants$. From this figure, we can discern that cases 2 and 4 have constant FORs just as every other measure has been constant. Cases 3, 5 and 6 appear to vary in FOR. for different $P(VAR|HCM)$ and $\#\ of\ variants$ combinations.

Figure 48 displays how FOR changes with increasing $\#\ of\ varaints$ for three different constant values of $P(VAR|HCM)$ of 0.5, 0.7 and 0.9. For cases 3, 5, and 6, FOR does not appear to vary with the $\#\ of\ varaints$, and all cases appear to have a slope of zero. Case 5 appears to consistently have the highest FOR, followed by Case 3, and then Case 6. This is likely due to the fact that cases 3 and 5 have an echocardiogram "check" that may increase the number of false negatives. Additionally, FOR seems to decrease for an increased value of $P(VAR|HCM)$, as the slopes remain the same but the y-intercepts change.

Figure 49 displays how FOR changes with increasing $P(VAR|HCM)$ for four constant values of $\#\ of\ varaints$ of 100, 200, 300 and 400. A negative slope can be seen in all figures: a decrease in FOR with increasing $P(VAR|HCM)$, likely due to the fact that less individuals with HCM are not picked up by genetic screening with an increased $P(VAR|HCM)$ because more individuals with HCM have a pathogenic variant. Case 6



(a) Case 2
σ: {1e-4, 2e-4, 2e-4, 2e-4, 2e-4}

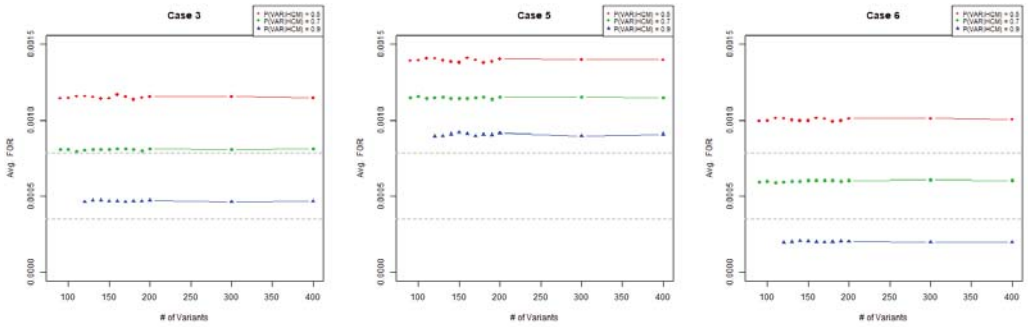
(b) Case 3
σ: {2e-4, 2e-4, 2e-4, 2e-4, 3e-4}

(c) Case 4
σ: {2e-4, 2e-4, 2e-4, 2e-4, 2e-4}

(d) Case 5
σ: {2e-4, 2e-4, 3e-4, 3e-4, 3e-4}

(e) Case 6
σ: {1e-4, 2e-4, 2e-4, 2e-4, 3e-4}

Figure 47: Heatmaps of the average FOR for each Officer case. Standard deviation summary given as: σ: {min, 25th quantile, median, 75th quantile, maximum}.



(a) Case 3

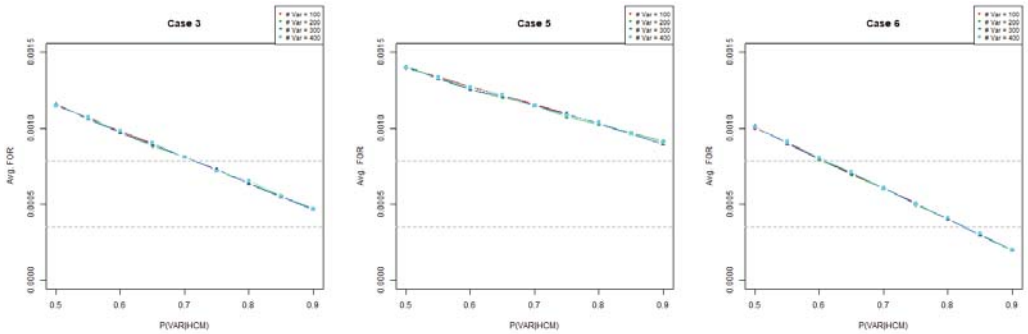
(b) Case 5

(c) Case 6

Figure 48: FOR, where the *# of variants* were changed for three different constant values of $P(VAR|HCM)$. Notice that the slopes of the lines are approximately zero. Increasing $P(VAR|HCM)$ shifts the curves down. Lower dotted grey line is the average value of FOR for Case 2, upper dotted grey line is the average value of FOR for Case 4.

appears to have the greatest slope and y-intercept, followed by Case 3 and then Case 5 (likely due to the more selective echocardiogram follow-up). Additionally, the line does not appear to change at all with different values of *# of varaints*, indicating the FOR is independent of the *# of varaints*.

The two grey dotted lines on Figures 48 and 49 represent the FORs of Case 4 (upper line) and Case 2 (lower line). Case 2 has a lower FOR likely because its echocardiogram is less specific and more sensitive than the one used in Case 4. Cases 5 and 3 never achieve values of FOR below the average values of their respective echocardiograms (Case 2 for Case 3 and Case 4 for Case 5). However, Case 3 appears to achieve an FOR below Case 4 above $P(VAR|HCM) = 0.7$. Case 6 appears to achieve an FOR below Case 4 above $P(VAR|HCM) = 0.6$ and below Case 2 above $P(VAR|HCM) = 0.8$.



(a) Case 3 (b) Case 5 (c) Case 6

Figure 49: FOR, where the $P(VAR|HCM)$ was changed for four different constant values of $\#\ of\ variants$. Cases 3, 5 and 6 all have negatives slopes, with the largest magnitude of slope of Case 6, followed by cases 3 and then 5. Notice how FOR does not change with changing values of $\#\ of\ variants$. Lower dotted grey line is the average value of FOR for Case 2, upper dotted grey line is the average value of FOR for Case 4.

9.2 Performance of Cases: Preventing Death

Ultimately, the goal of the screening is not to look for individuals with HCM, but rather to prevent death due to sudden cardiac death (SCD). We look at both the total number of deaths per each case and the percent of individuals who are discharged that would have died had they been in the military.

It is important to note that when we say "prevent" death, we hope to both avoid the cost of an individual dying in the military due to SCD as well as allow the individual to pursue the avenue to proper treatment of their HCM to prevent SCD in the future. The military may be concerned about the cost associated with an individual dying in the military, however the individual discharged due to HCM that lives because of knowledge of their diagnosis due to the screening implemented by the military is something to consider as a "benefit" as well.

9.2.1 Number of Deaths

The average total number of deaths over the 1000 officer simulations per each case per each $P(VAR|HCM)$ and $\#\ of\ variants$ combinations are illustrated as heatmaps in Figure 50. It is important to note that Case 1 represents the average number of individuals that die from HCM in the military given no intervention whatsoever. The number of individuals saved from a screening case may be calculated by:

$$deaths\ prevented = individuals\ die\ in\ Case\ 1 - individuals\ die\ in\ screening\ Case\ X \tag{19}$$

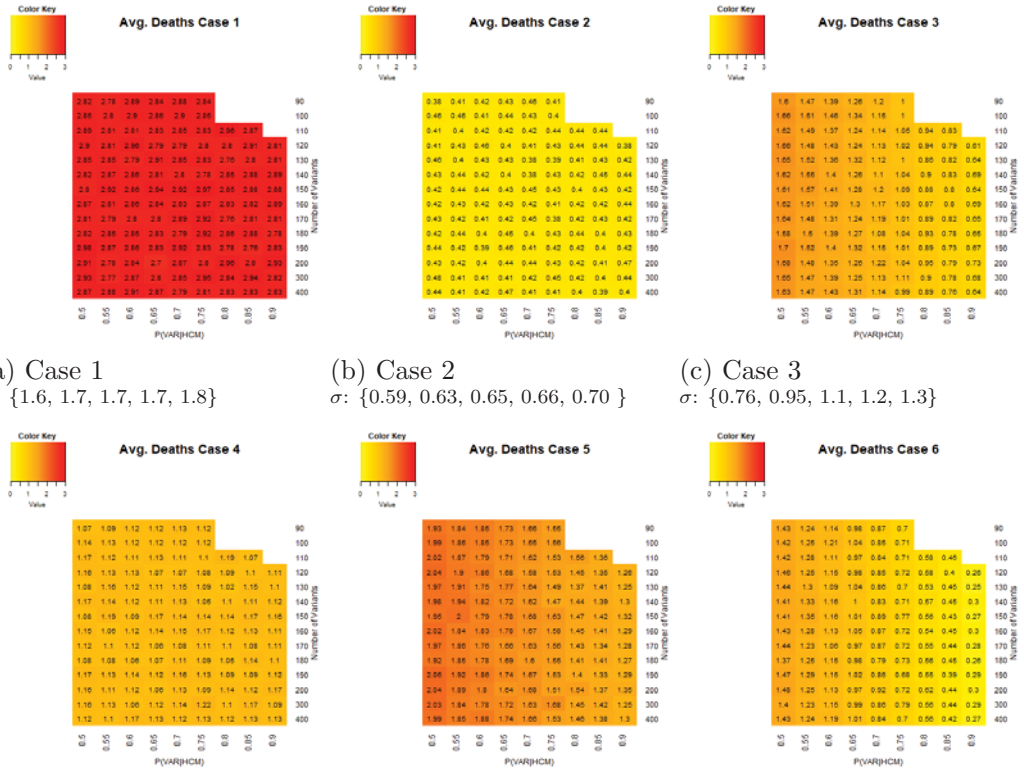
In this section, we will not analyze the number of deaths prevented, but rather will view the best performing screening test as the test that has the *least* number of deaths in the military.

Figure 51 displays how the $\#\ of\ deaths$ changes with changing $\#\ of\ variants$ and constant $P(VAR|HCM)$ values of 0.5, 0.7 and 0.9 for cases 3, 5 and 6. It can be seen for all three of these cases that the number of deaths does not change significantly for changing $\#\ of\ variants$, but the y-intercept of the lines increase for a smaller $P(VAR|HCM)$. Case 5 appears to have the highest $\#\ of\ deaths$ for each value of $P(VAR|HCM)$, and Case 6 appears to have the lowest $\#\ of\ deaths$ for each value of $P(VAR|HCM)$, likely due to the echocardiogram follow-up removing some individuals with HCM as false negatives.

In Figure 52, the number of deaths is seen to decrease for an increasing $\#\ of\ variants$, indicating that as the genetic tests are able to identify more individuals with HCM, the number of people who die from the condition decrease. The greatest slope was seen for Case 6, followed by cases 3 then 5, and the constant $\#\ of\ variants$ value used did not change the y-intercept or slope of the line.

Also identified in these figures are the average number of deaths for cases 2, 4 and 1. Case 2 is displayed as the lower dotted grey line. Cases 3 and 5 never have values below Case 2, and Case 6 only is below Case 2 for high $P(VAR|HCM)$ values. The average number

of deaths for Case 4 is sown as the upper grey line in Figures 51 and 52. Case 5 never goes below this line, however Case 3 has less deaths than Case 5 at a $P(VAR|HCM)$ of approx. 0.7, and Case 6 has less deaths than Case 5 at a $P(VAR|HCM)$ of approx. 0.6. The average deaths for Case 1 is shown as the red dotted line at the top of the figures. Screening tests better prevent SCD the further they are below this red line.



(a) Case 1
σ: {1.6, 1.7, 1.7, 1.7, 1.8}

(b) Case 2
σ: {0.59, 0.63, 0.65, 0.66, 0.70 }

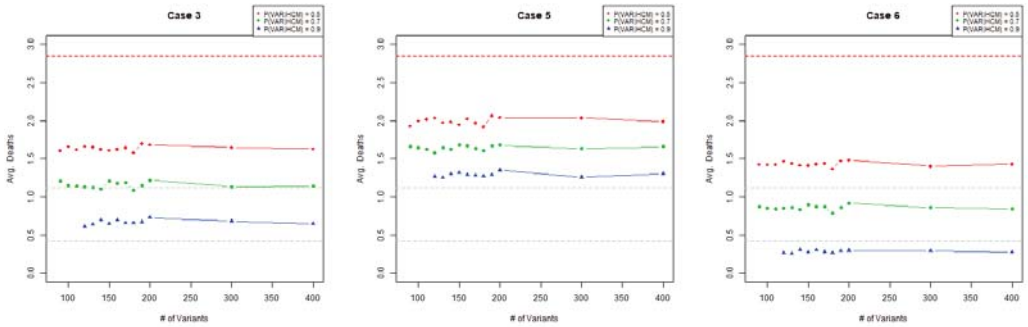
(c) Case 3
σ: {0.76, 0.95, 1.1, 1.2, 1.3}

(d) Case 4
σ: {0.99, 1.0, 1.1, 1.1, 1.1}

(e) Case 5
σ: {1.1, 1.2, 1.3, 1.4, 1.5}

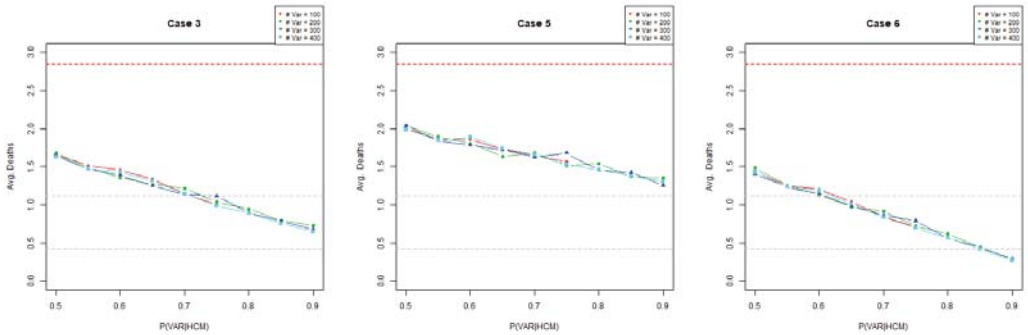
(f) Case 6
σ: {0.5, 0.8, 0.9, 1.1, 1.2}

Figure 50: Heatmaps of the average number of deaths for each Officer case. Standard deviation summary given as: σ: {min, 25th quantile, median, 75th quantile, maximum}.



(a) Case 3 (b) Case 5 (c) Case 6

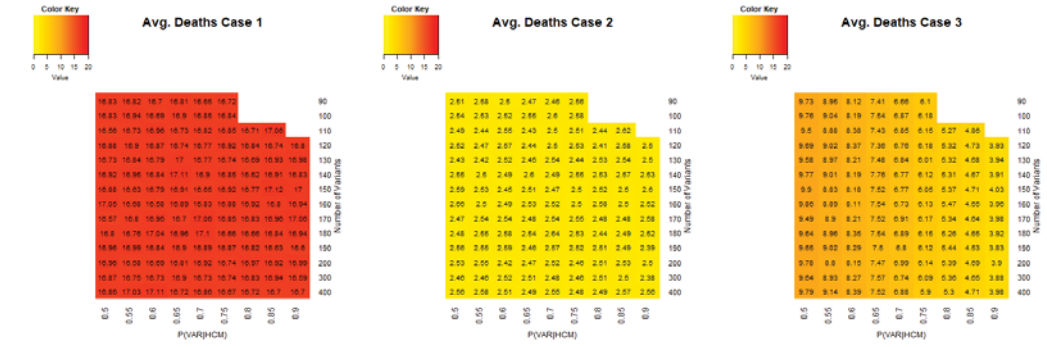
Figure 51: deaths, where the $\#\ of\ variants$ were changed for three different constant values of $P(VAR|HCM)$. Notice how the cases do not appear to vary with $\#\ of\ variants$ but the curves shift down with increasing $P(VAR|HCM)$. Upper dotted red line is the average deaths from Case 1, the middle grey line is the average deaths from Case 4, and the lower dotted grey line is the average deaths from Case 2.



(a) Case 3 (b) Case 5 (c) Case 6

Figure 52: deaths, where the $P(VAR|HCM)$ was changed for four different constant values of $\#\ of\ variants$. Cases 3, 5 and 6 have negative slopes, with Case 6 having a greater slope. Upper dotted red line is the average deaths from Case 1, the middle grey line is the average deaths from Case 4, and the lower dotted grey line is the average deaths from Case 2.

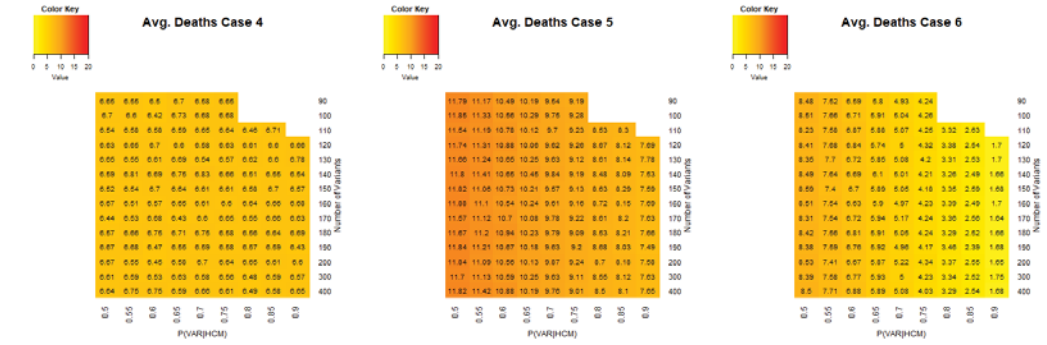
We also include the results from the enlisted simulations. Displayed in Figure 53, the heatmaps for the average death value for each $P(VAR|HCM)$ and $\#\ of\ variants$ combinations in the 1000 enlisted simulations are displayed.



(a) Case 1
σ: {3.8, 4.0, 4.1, 4.2, 4.3}

(b) Case 2
σ: {1.5, 1.6, 1.6, 1.6, 1.7}

(c) Case 3
σ: {1.9, 2.3, 2.6, 2.9, 3.2}



(d) Case 4
σ: {2.4, 2.5, 2.6, 2.6, 2.8}

(e) Case 5
σ: {2.7, 2.9, 3.2, 3.3, 3.6}

(f) Case 6
σ: {1.2, 1.9, 2.3, 2.7, 3.0}

Figure 53: Heatmaps of the average deaths for each enlisted case. Standard deviation summary given as: σ: {min, 25th quantile, median, 75th quantile, maximum}.

Due to the larger size of the enlisted population, the deaths would be expected to be greater. However, enlisted individuals only spend an average of 7 years in the military compared to 11 for officers, and so an enlisted individual who has HCM would have a decreased chance of dying of SCD in the military because the chance of SCD due to HCM is 0.0081 *per year*. Additional enlisted graphs can be found in Appendix B.

The same overall trends exist for the enlisted cases as for the officer cases. However, unlike in previous situations, where the enlisted absolute values were more of a direct reflection of the ratio of the enlisted population to the officer population, the absolute values in these cases are less than that ratio would predict due to the less number of years the enlisted spend in the military on average.

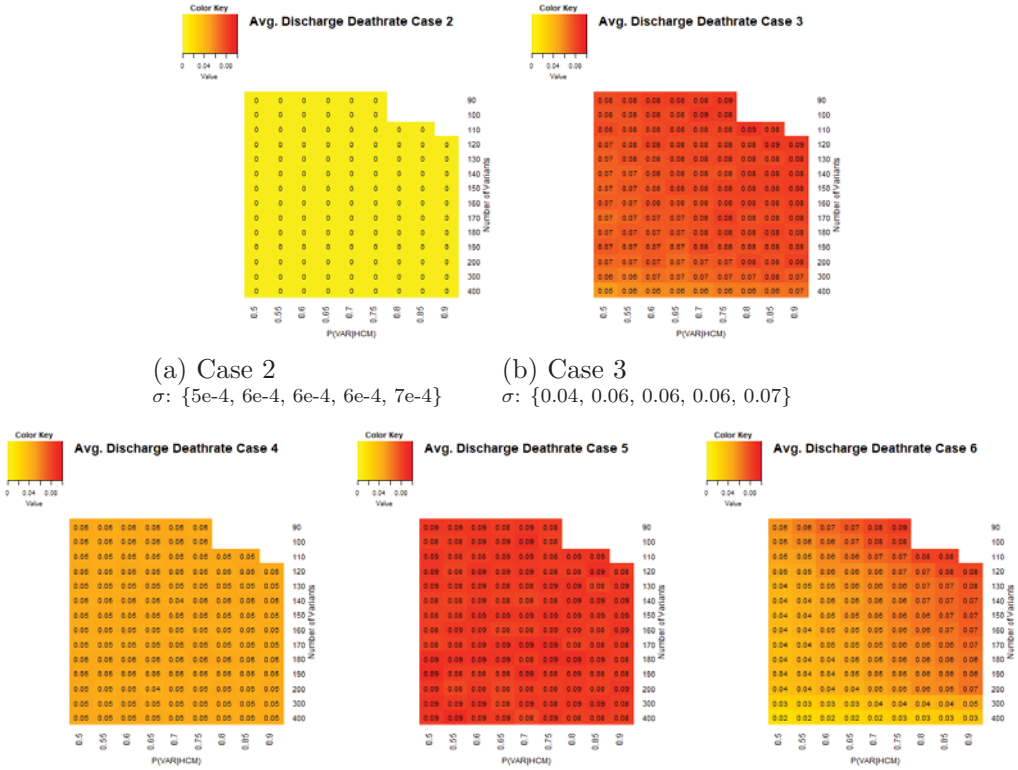
9.2.2 Fraction of Deaths Prevented For Discharged Individuals

We also explore the proportion of individuals who are discharged for each case that would have died of sudden cardiac death had they been in the military. The discharge deathrate is equal to:

$$Discharge\ Deathrate\ (DDrate) = \frac{\#\ of\ deaths\ prevented}{\#\ of\ individuals\ discharged} \tag{20}$$

Where the # of deaths prevented is equal to the number of individuals who would have died during military service had they not been discharged as described in Equation 19.

In Figure 54, displayed are the heatmaps for the average value for each of the $P(VAR|HCM)$ and $\#\ of\ variant$ combinations among the 1000 officer simulations. It can be seen here that cases 2, 4 and 5 do not appear to vary, similarly to other measures listed before.



(a) Case 2
σ: {5e-4, 6e-4, 6e-4, 6e-4, 7e-4}

(b) Case 3
σ: {0.04, 0.06, 0.06, 0.06, 0.07}

(c) Case 4
σ: {0.03, 0.03, 0.04, 0.04, 0.04}

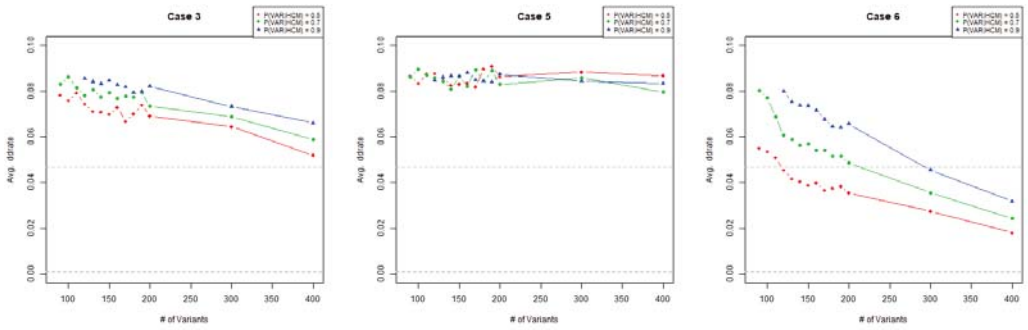
(d) Case 5
σ: {0.07, 0.07, 0.08, 0.09, 0.1}

(e) Case 6
σ: {0.01, 0.03, 0.04, 0.04, 0.06}

Figure 54: Heatmaps of the average discharge deathrate for each Officer case. Standard deviation summary given as: σ: {min, 25th quantile, median, 75th quantile, maximum}.

In Figure 55, the change in the discharge deathrate for the change in the $\#\ of\ variants$ is shown. It can be seen that for cases 3 and 6, the slopes are negative. Additionally, the curves appear to shift up for higher $P(VAR|HCM)$ values. Case 5 does not appear to change. These patterns are likely due to the fact that increasing the $\#\ of\ variants$ decreases the specificity for cases 3 and 6, which causes more individuals without HCM

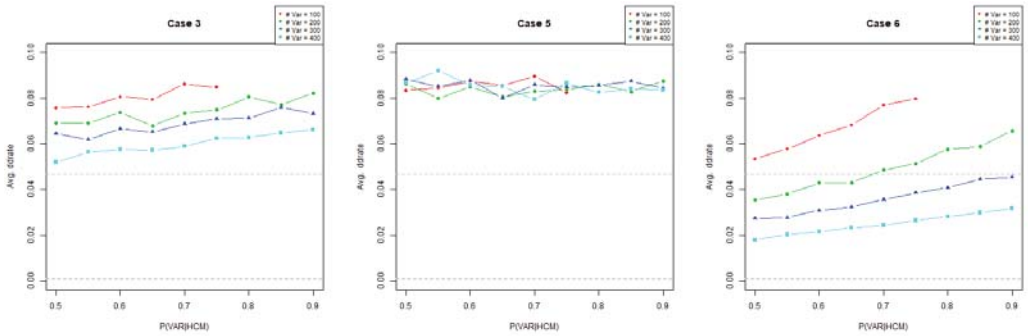
to be discharged, correlating to a lower discharge deathrate.



(a) Case 3 (b) Case 5 (c) Case 6

Figure 55: discharge deathrate, where the $\#\ of\ variants$ were changed for three different constant values of $P(VAR|HCM)$. Notice that the slopes of the lines for Case 6 are the most negative, and the slopes of the lines for Case 3 have smaller magnitudes, while Case 5 has nearly flat lines. Increasing $P(VAR|HCM)$ shifts the curves up. Lower Dotted grey line is the average value of DDrate for Case 2, upper dotted grey line is the average value of DDrate for Case 4.

In Figure 56, the change in the discharge deathrate for the change in $P(VAR|HCM)$ is displayed. In these figures, the slopes for cases 3 and 6 are both positive. Additionally, as the $\#\ of\ variants$ increases, the discharge deathrate curve shifts down for cases 3 and 5. The slope and curve shifts are more dramatic for Case 6 than Case 3, however. Case 5 appears to have a slope of zero and the line appears not to change for all cases.



(a) Case 3 (b) Case 5 (c) Case 6

Figure 56: discharge death rate, where the $P(VAR|HCM)$ was changed for four different constant values of $\#\ of\ variants$. Cases 3 and 6 have positive slopes, with Case 6 having a greater slope and more variation in intercepts for different values of $\#\ of\ variants$. Case 5 has flat lines. The lower dotted grey line represents the average value for the DDrate of Case 2, the upper dotted grey line represents the average value for the DDrate of Case 4.

The average discharge deathrate for cases 2 and 4 are displayed as the lower and upper grey lines, respectively, on Figures 55 and 56. Cases 3 and 5 surpasses these two averages

for all $\#\ of\ variants$ and $P(VAR|HCM)$ combinations. Case 6, however, only surpasses Case 4 for high $P(VAR|HCM)$ and low $\#\ of\ variants$ combinations.

10 Cost of Screening Tests

We determined through the results of this simulation which cases, and dependent on which variables, would confer a monetary benefit or cost to the military if performed. "cost" in this section only refers to the monetary cost associated with the screening tests or with individuals dying from sudden cardiac death (SCD) due to HCM in the military.

With regard to cost, the enlisted and officer simulations may incur vastly different costs, due to the differentials in their population sizes, cost of training, and years in service. Additionally, combining the officer and enlisted cases may further change the cost analysis. We explore each option in depth in this section.

All costs provided in this report are in the United States Dollar value at March of 2018.

10.1 Cost of Doing Nothing

Analysis of the monetary cost of the screening test cases was performed by relating the cost of a test to the cost of "doing nothing," or the cost of Case 1. We did this by determining the Net benefit of each screening test, which was:

$$Net\ benefit = Cost\ Case\ 1 - Cost\ Case\ X \tag{21}$$

Where X is a screening case (2-6). The cost of Case 1 is the status quo: the cost that the military is incurring currently. The cost of each cases includes the cost of screening and the cost associated with individuals that die because they are not picked up by the screening. If the cost of case X is lower than the cost of Case 1, the military will save money, and the Net benefit will be positive. If the cost of case X is more than the cost of Case 1, the military will loose money and the Net benefit will be negative. Thus, we are trying to determine if for any of the cases the Net benefit is positive, and under what conditions the Net benefit may be maximized.

The cost of Case 1 would expected to stay relatively constant for each officer and enlisted simulations. Figure 57 shows the enlisted and officer costs of doing nothing. It is important to note that despite having similar costs for Case 1, the officer and enlisted simulations did not arrive at the same costs or the same mechanisms for achieving the costs. The reason for the officer and enlisted similarity in costs is due to the greater cost of training an officer (around 15 times greater) than training an enlisted member, yet the decreased population of officers compared to enlisted.

(a) Officer Cost Case 1
$\sigma : \{2e6, 2e6, 2e6, 2e6, 2e6\}$

(b) Enlisted Cost Case 1
$\sigma : \{6e5, 6e5, 6e5, 6e5, 7e5\}$

Figure 57: Average cost of doing nothing (Case 1). Enlisted and officer simulations have similar, but not equal costs. More enlisted members die, but the cost per death of enlisted member is lower than the cost per death of an officer due to the decreased training costs. Standard deviation summary given as: σ: {min, 25th quantile, median, 75th quantile, maximum}.

10.2 Cost of Officer Simulation

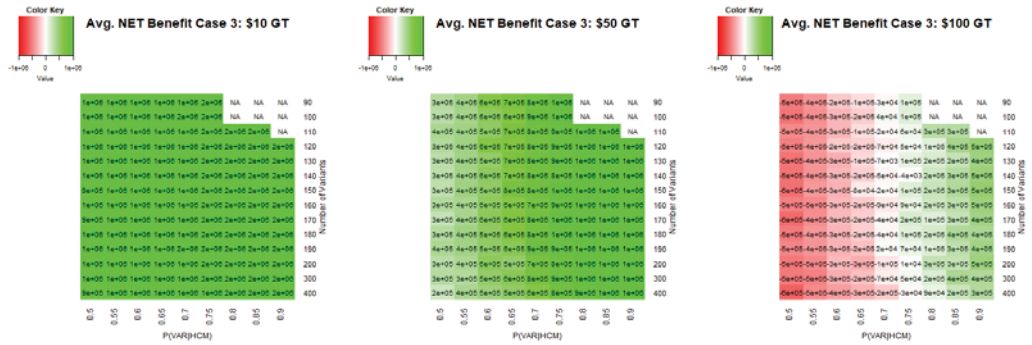
Here, we use the officer simulation to determine what would be the most effective case from a cost perspective.

10.2.1 Net Benefit Case 3: Officer

We begin our genetic cost analysis with Case 3 for officers: a genetic test followed by a high-accuracy echocardiogram. We first took the Net benefit of twelve different genetic test (GT) costs: \$10, \$50, \$100, \$200, \$300, \$400, \$500, \$600, \$700, \$800, \$900, and \$1000. We displayed the average Net benefit among the 1000 officer simulations for each combination of $P(VAR|HCM)$ and $\#\ of\ variants$ for each of the three different GT costs where Net benefit is positive, displayed in Figure 58.

The military incurs no benefit whatsoever when the genetic test cost is \$200 and above for Case 3. However, as seen in Figure 58, a positive Net benefit is realized at a GT cost of \$100 for some values of $P(VAR|HCM)$.

We also look to see how the Net benefit varies with different $P(VAR|HCM)$ and $\#\ of\ variants$ values. In Figure 59a, we see that the $\#\ of\ variants$ appears to have little effect on the Net benefit of Case 3, but may cause the slope to be slighly negative where an increased $\#\ of\ variants$ causes a decrease in Net benefit. However, from Figure 59b, we can see that with an increased $P(VAR|HCM)$, the Net benefit for Case 3 increases, crossing zero and yielding a positive value for the \$100 and cheaper genetic tests.



(a) \$10 Genetic Test
σ : {1e6, 1e6, 1e6, 1e6, 2e6}

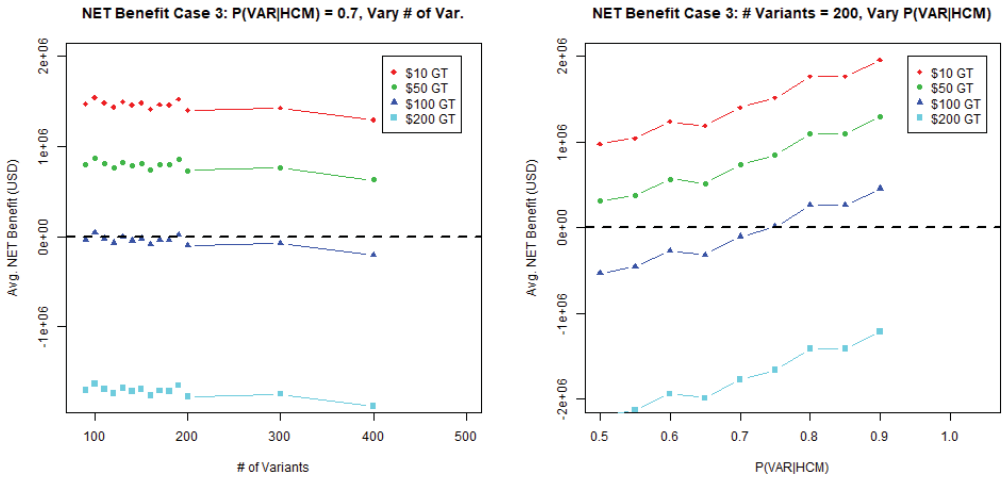
(b) \$50 Genetic Test
σ : {1e6, 1e6, 1e6, 1e6, 2e6}

(c) \$100 Genetic Test
σ : {1e6, 1e6, 1e6, 1e6, 2e6}

Figure 58: Heatmaps of the average Net benefit for officer Case 3 where Net benefit is realized. Standard deviation summary given as: σ: {min, 25th quantile, median, 75th quantile, maximum}.

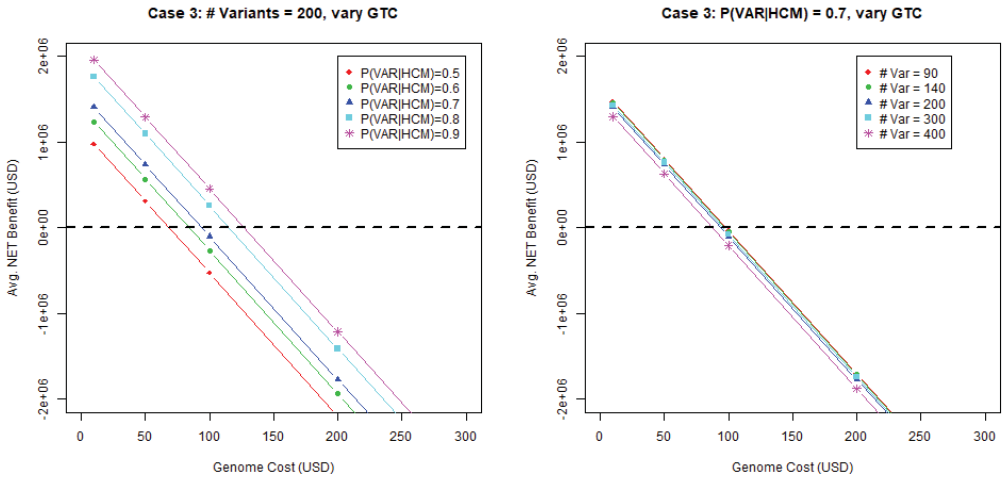
Finally, we attempt to determine the cost of the genetic test at which for a given $P(VAR|HCM)$ and $\#\ of\ variants$ the Net benefit equal zero, or the military will "break even" in regards to the benefit of individuals saved and the cost of the test. A genetic test cost below this value and at the same combination of $\#\ of\ variants$ and $P(VAR|HCM)$ will result in a positive Net benefit (military will *make* money from implementation), and a genetic test cost above this value will result in a negative Net benefit (military will *lose* money from implementation). We did this by plotting, for one combination of $P(VAR|HCM)$ and $\#\ of\ variants$, the average Net benefit vs. the genome cost. We then fitted a regression line to the points, and found the x-intercept of the line. This x-intercept represents the genetic test cost for that particular $P(VAR|HCM)$ and $\#\ of\ variants$ combination that the military will "break even" at. An example of this procedure is highlighted in Figure 60.

From the procedure outlined above, "Break-Even" genetic test costs were found for each $P(VAR|HCM)$ and $\#\ of\ variants$ combinations, displayed in Figure 61. From this figure, it can be determined that at what point, when a genetic test is at a certain cost, this case may be realistic to implement.



(a) Vary $\#\ of\ variants$ (b) Vary $P(VAR|HCM)$

Figure 59: 59a displays how Net benefit of officer Case 3 differs with changing $\#\ of\ variants$. Notice how the slope appears to be zero, or slightly negative. The \$100 genetic test straddles the \$0 Net benefit line. Figure 59b displays how Net benefit changes with a change in $P(VAR|HCM)$. Notice how the slopes are positive.



(a) Example 1 (b) Example 2

Figure 60: From these plots, where each line intersects zero (the dotted black line) is considered the "break even" cost. This was found for each $P(VAR|HCM)$ and $\#\ of\ variants$ combination.

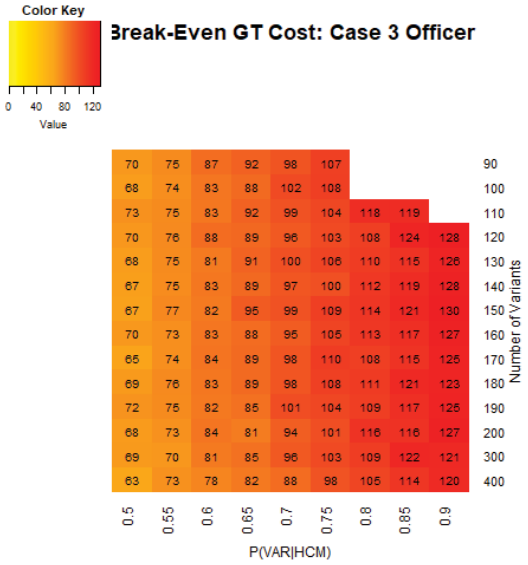


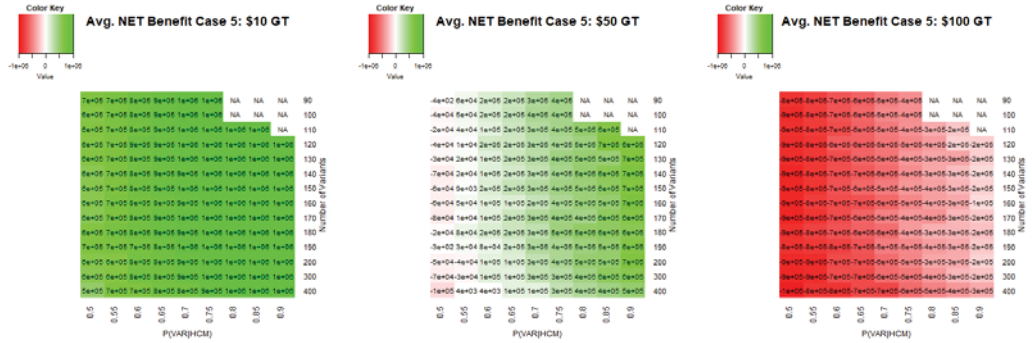
Figure 61: "Break-Even" genetic test costs for Officer Case 3. All costs are in USD value at March of 2018.

10.2.2 Net Benefit Case 5: Officer

We perform this analysis as we did with officer Case 3. Figure 62 displays the heatmaps for the average Net benefit amount 1000 simulations for each $P(VAR|HCM)$ and $\#\ of\ variants$ combinations. This figure shows that Net benefit does not generally occur until a \$50 genetic test cost is implemented.

Figures 63a and 63b display how the Net benefit of Case 5 changes with $P(VAR|HCM)$ and $\#\ of\ variants$. The trends remain the same between cases 3 and 5: a slightly negative slope for changing $\#\ of\ varaints$, and positive slope for changing $P(VAR|HCM)$. However, the magnitudes of the slopes are lower for Case 5 than Case 3. This can be explained by the much more selective echocardiogram that Case 5 undergoes relative to Case 3, which decreases its sensitivity and thus does not allow as many people to be detected and saved from SCD relative to Case 3.

In Figure 64, the "break-even" values for officer Case 5 are displayed. Note that these values follow the same trends, but are less than the values for Case 3.

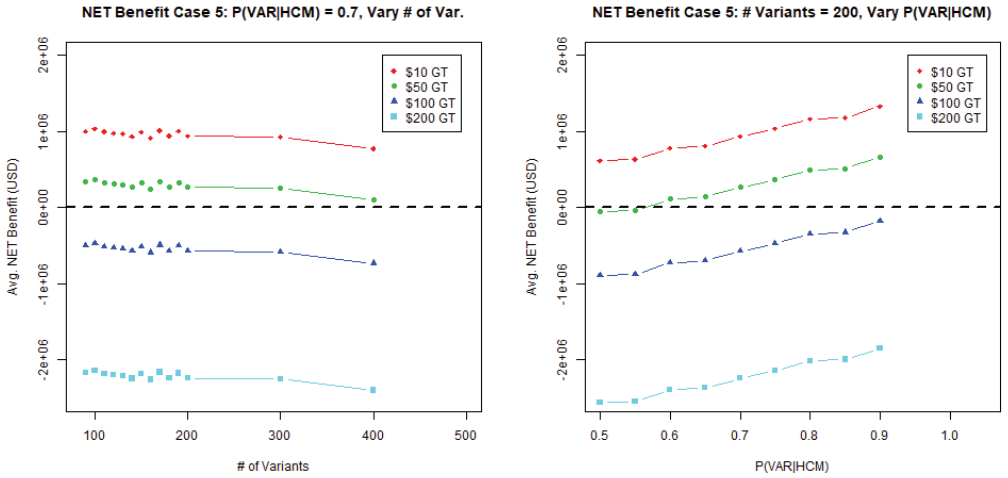


(a) \$10 Genetic Test
σ : {9e5, 1e6, 1e6, 1e6, 1e6}

(b) \$50 Genetic Test
σ : {9e5, 1e6, 1e6, 1e6, 1e6}

(c) \$100 Genetic Test
σ : {9e5, 1e6, 1e6, 1e6, 1e6}

Figure 62: Heatmaps of the average Net benefit for officer Case 5. Standard deviation summary given as: σ: {min, 25th quantile, median, 75th quantile, maximum}.



(a) Vary # *of variants* (b) Vary $P(VAR|HCM)$

Figure 63: Net benefit graphs for officer Case 5, Notice how these trends follow the trends in officer Case 3, with the slope slightly negative for Figure 63a and positive for 63b. However, the Net benefit appears to be less compared to Case 3.

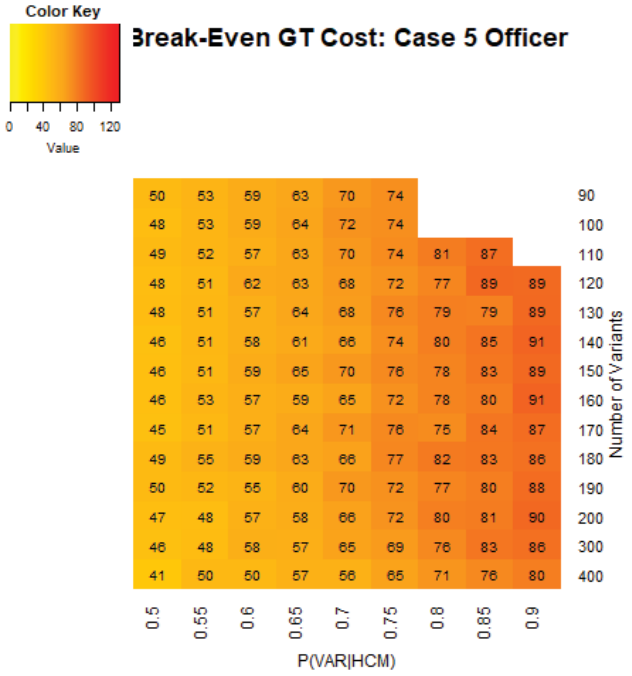


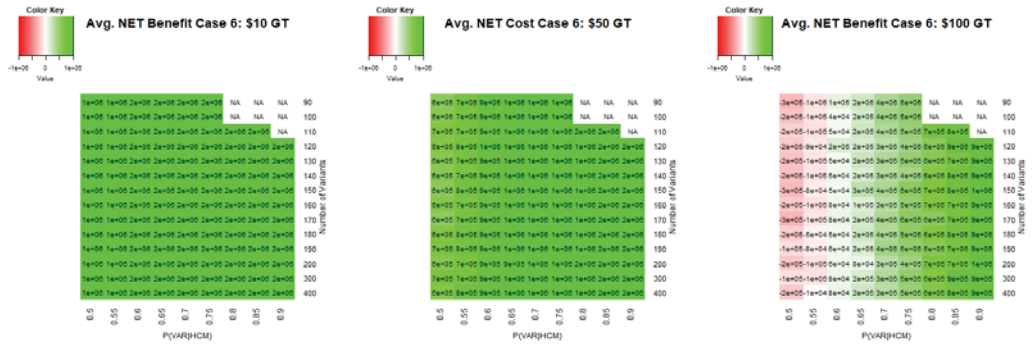
Figure 64: "Break-Even" genetic test costs for Officer Case 5.

10.2.3 Net Benefit Case 6: Officer

Heatmaps for officer Case 6 for the average Net benefit over 1000 simulations for each $P(VAR|HCM)$ and $\#\ of\ variants$ combination are shown in Figure 65. It can be seen from these heatmaps that the Net benefit reaches a positive value for more of the \$100 genetic test $P(VAR|HCM)$ and $\#\ of\ variants$ combinations than Case 5 or Case 3. This is likely due to the fact that there is no secondary "check" on the test, which costs additional money and causes some individuals with HCM to be erroneously retained after testing positive for a pathogenic variant.

From Figures 66a and 66b, it can be seen that the Net benefit does not appear to change with an increased $\#\ of\ variants$, and the Net benefit appears to increase with an increased $P(VAR|HCM)$. The reason why the Net benefit value does not change with $\#\ of\ variants$ can be explained by the fact that no additional costs are incurred when an individual tests positive for a genetic test, unlike in cases 3 and 5 which require echocardiograms, and so more people testing positive for a genetic test when more variants are present will not affect the Net benefit of Case 6.

Figure 67 displays the "break-even" genetic test costs for Case 6. These appear to be larger than for cases 3 and 5, indicating that a more expensive genetic test will yield more benefit for Case 6 than cases 3 or 5.

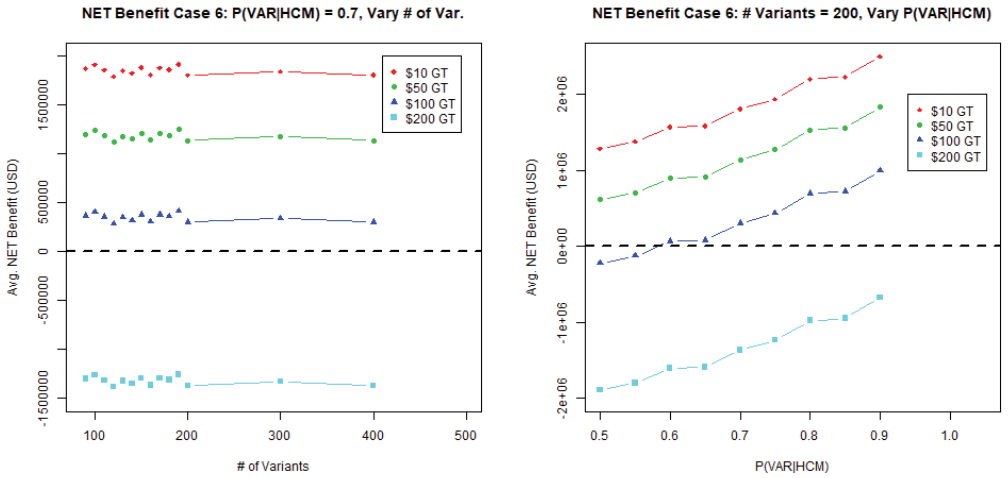


(a) \$10 Genetic Test
σ : {1e6, 1e6, 1e6, 2e6, 2e6}

(b) \$50 Genetic Test
σ : {1e6, 1e6, 1e6, 2e6, 2e6}

(c) \$100 Genetic Test
σ : {1e6, 1e6, 1e6, 2e6, 2e6}

Figure 65: Heatmaps of the average Net benefit for officer Case 6. Standard deviation summary given as: σ: {min, 25th quantile, median, 75th quantile, maximum}.



(a) Vary $\#\ of\ variants$ (b) Vary $P(VAR|HCM)$

Figure 66: Change in Net benefit for officer Case 6 with varying $\#\ of\ variants$ (Figure 66a and varying $P(VAR|HCM)$ (Figure 66b. Note how the slopes appear to be zerowith varying $\#\ of\ variants$, and positive for varying $P(VAR|HCM)$. In this case the entire $100 GT is above a Net benefit of 0.

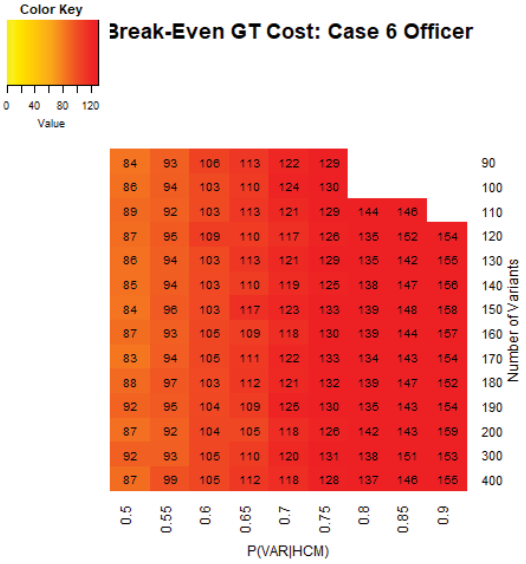
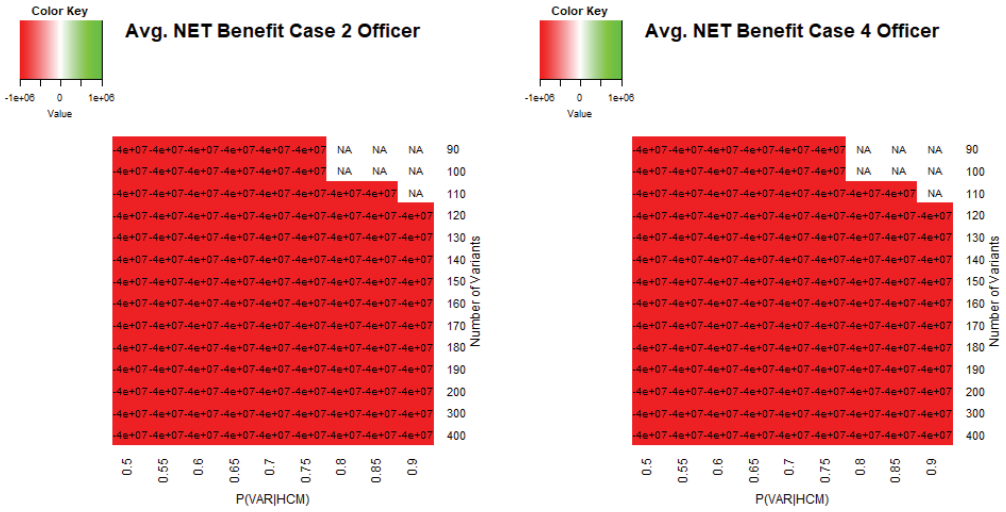


Figure 67: "Break-Even" genetic test costs for Officer Case 6.

10.2.4 Comparing Screening Costs: Officer Simulation

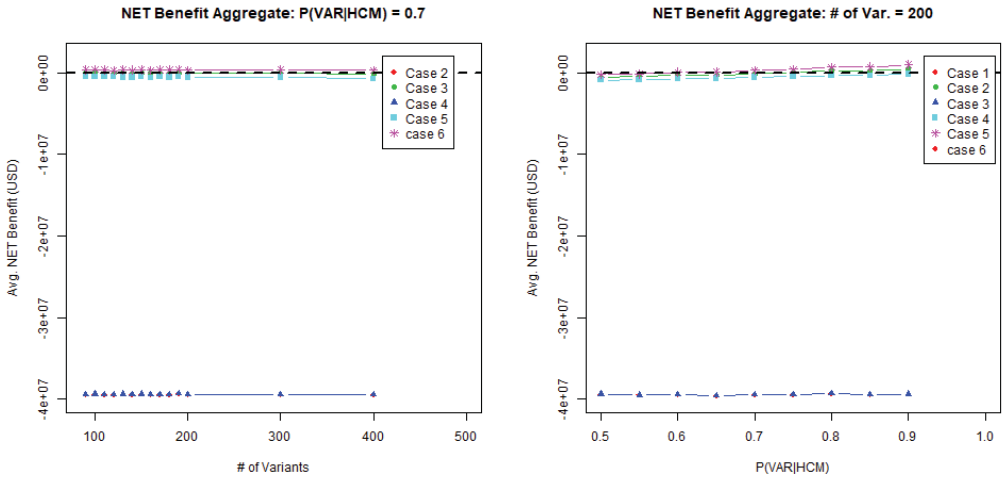
Now that the genetic tests (cases 3, 5 and 6) have been analyzed, we look to analyze the non-genetic tests (cases 2 and 4) and compare the costs of these non-genetic tests to the genetic tests. Figure 68 displays heatmaps for the average Net benefit over the 1000 simulations of the cost of Case 2 and Case 4 for each $P(VAR|HCM)$ and $\#\ of\ variants$ combination. Figure 69 shows the Net benefit of cases 2 and 4 in comparison to cases 3, 5 and 6 at a \$100 genetic test. It can be seen that the Net benefit of cases 2 and 4 is much lower than that of Case 3, 5 and 6 at a GT cost of \$100. However, increasing the \$GT cost increases the cost of the genetic test cases. Overall, echocardiogram only tests are much more costly than genetic tests.



(a) Officer Cost Case 2
σ : $\{1e6, 2e6, 2e6, 2e6, 2e6\}$

(b) Officer Cost Case 4
σ : $\{1e6, 2e6, 2e6, 2e6, 2e6\}$

Figure 68: Average Net benefit of Case 2 and Case 4 (officer simulation). Standard deviation summary given as: σ: {min, 25th quantile, median, 75th quantile, maximum}.



(a) vary # of Var.

(b) Vary $P(VAR|HCM)$

Figure 69: Average Net benefit of cases 2, 3, 4, 5 and 6 on two graphs with varying $\#\ of\ variants$ and $P(VAR|HCM)$. It can be seen that cases 2 and 4 do not change with either $\#\ of\ variants$ nor $P(VAR|HCM)$, and that their Net benefit is much less than any of the genetic tests at the particular genetic cost. This is due to the high cost of the echocardiogram.

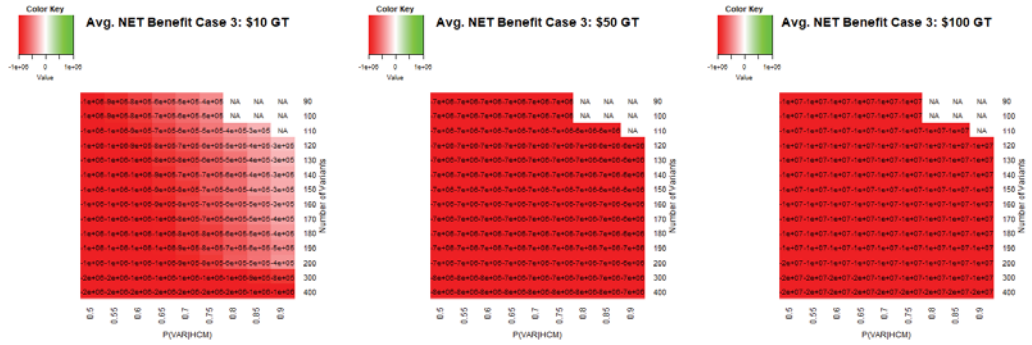
10.3 Enlisted Simulation Cost Results

10.3.1 Enlisted Case 3

Just as analyzed in the officer Case 3, in Figure 70, three heatmaps for the cheapest GT costs for enlisted Case 3 are displayed. From these heatmaps, it can be seen that the enlisted Case 3 confers benefit at a much smaller GT cost than officer Case 3 did, which looks to be below a $10 genetic test.

Figure 71a displays how the Net benefit changes with changing $\#\ of\ variants$. The slopes of the lines appear to be negative, indicating that benefit decreases as the $\#\ of\ variants$ increases, likely due to the need for more echocardiograms. In Figure 71b, the Net benefit appears to increase for a greater $P(VAR|HCM)$, likely due to more individuals with HCM being identified by the test.

In Figure 72, the "break-even" genetic test cost values for enlisted Case 3 are displayed. Note how much smaller these values are than for the officer case. Additionally, note how a few GT costs appear to be negative. The reason for this negative GT cost is because, when a large population of individuals who do not have HCM is required to have echocardiogram screening (more likely to happen when $P(VAR|HCM)$ is low and the $\#\ of\ variants$ is high), the cost of the follow-up echocardiograms themselves will cause a negative Net benefit, because so many follow-up echocardiograms are required. This is why a *negative* GT cost is required to counterbalance this inequality A negative GT cost indicates that not only the GT needs to be very low, but the echocardiogram test must be lower in cost as well.

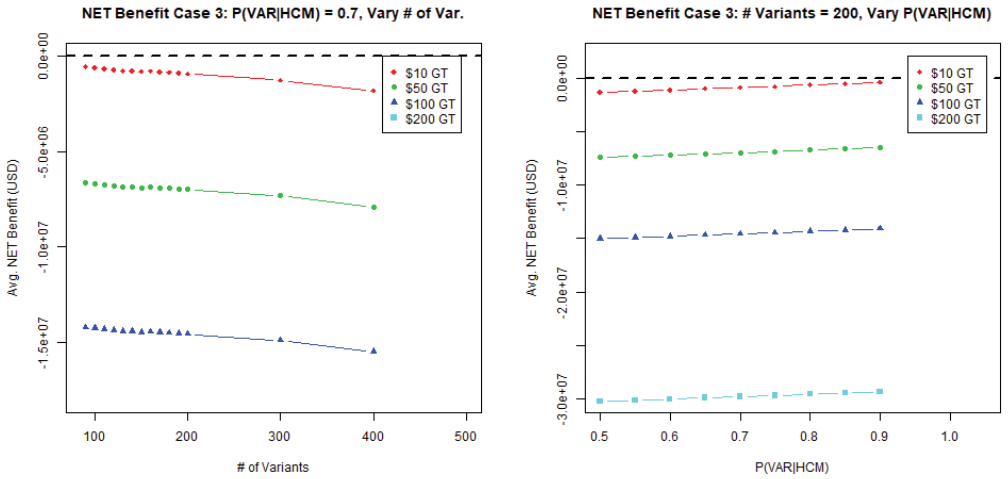


(a) $10 Genetic Test
σ : {4e5, 4e5, 5e5, 5e5, 6e5}

(b) $50 Genetic Test
σ : {4e5, 4e5, 5e5, 5e5, 6e5}

(c) $100 Genetic Test
σ : {4e5, 4e5, 5e5, 5e5, 6e5}

Figure 70: Heatmaps of the average Net benefit for enlisted Case 3. Standard deviation summary given as: σ: {min, 25th quantile, median, 75th quantile, maximum}.



(a) Vary # *of variants* (b) Vary $P(VAR|HCM)$

Figure 71: Change in Net Benefit for enlisted Case 3 with either changing # *of variants* or $P(VAR|HCM)$. Note how the trends are the same as in the officer simulation: decreasing benefit for increasing # *of variants* and increasing benefit for increasing $P(VAR|HCM)$, but absolute values are much smaller.

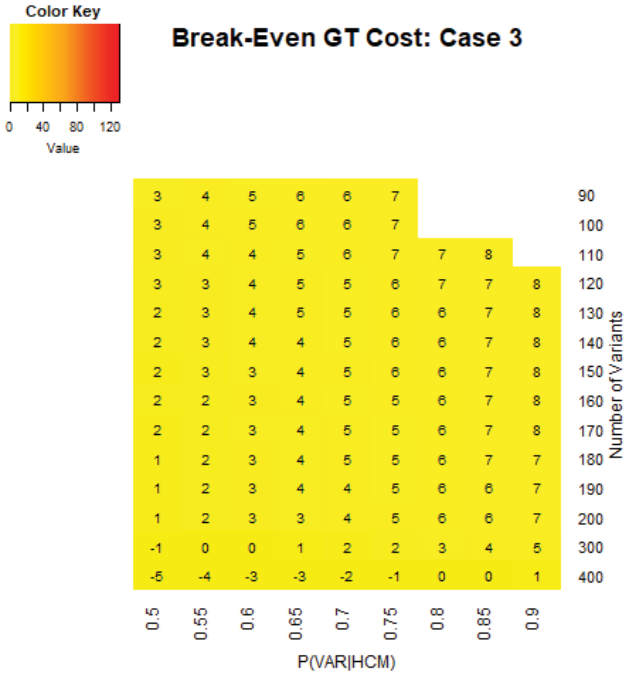


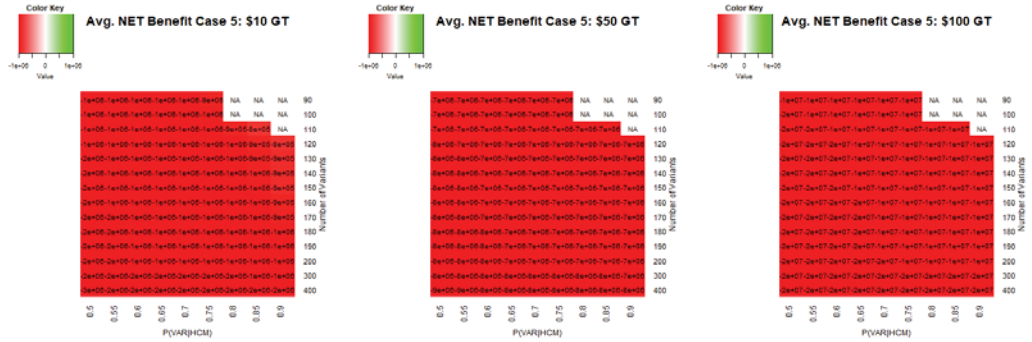
Figure 72: "Break-Even" genetic test costs for Enlisted Case 3.

10.3.2 Enlisted Case 5

In Figure 73, three heatmaps for the cheapest GT costs for enlisted Case 5 are displayed. From these heatmaps, it can be seen that the enlisted Case 5 confers benefit at a smaller GT cost than enlisted Case 3 did.

Figure 74a displays how the Net benefit changes with changing $\#\ of\ variants$. The slopes of the lines appear to be negative, indicating that benefit decreases as the $\#\ of\ variants$ increases, likely due to the need for more echocardiograms. In Figure 74b, the Net benefit appears to increase for a greater $P(VAR|HCM)$, likely due to more individuals with HCM being identified by the test.

In Figure 75, the "break-even" genetic test cost values for enlisted Case 5 are displayed. Note that these are smaller than enlisted Case 3.

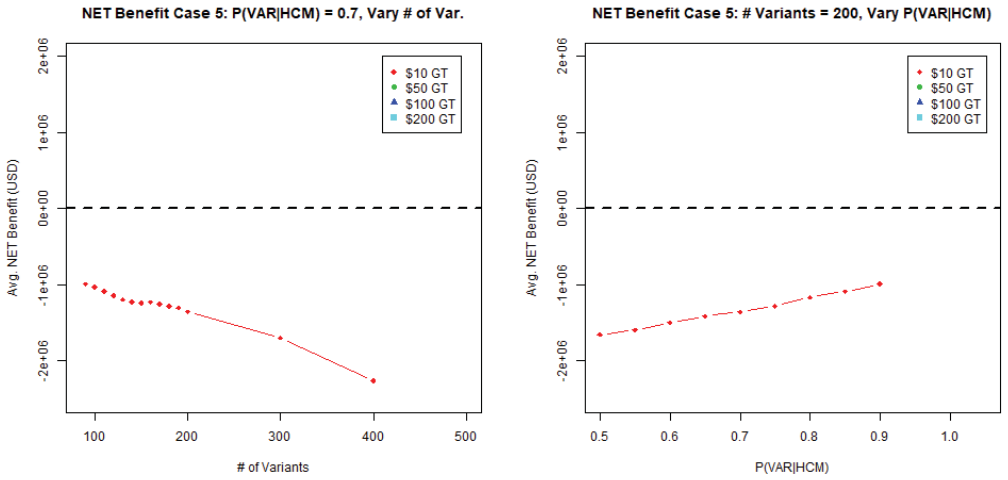


(a) \$10 Genetic Test
σ : {3e5, 4e5, 4e5, 4e5, 5e5}

(b) \$50 Genetic Test
σ : {3e5, 4e5, 4e5, 4e5, 5e5}

(c) \$100 Genetic Test
σ : {3e5, 4e5, 4e5, 4e5, 5e5}

Figure 73: Heatmaps of the average Net benefit for enlisted Case 5. Standard deviation summary given as: σ: {min, 25th quantile, median, 75th quantile, maximum}.



(a) Vary *# of variants* (b) Vary $P(VAR|HCM)$

Figure 74: Change in Net Benefit for enlisted Case 5 with either changing *# of variants* or $P(VAR|HCM)$. In Figure 74a, note how the Net benefit decreases as *# of varians* increases. In Figure 74b, note how the Net benefit increases for an increase in $P(VAR|HCM)$. Additionally, note that only the $GT cost is near positive Net benefit.

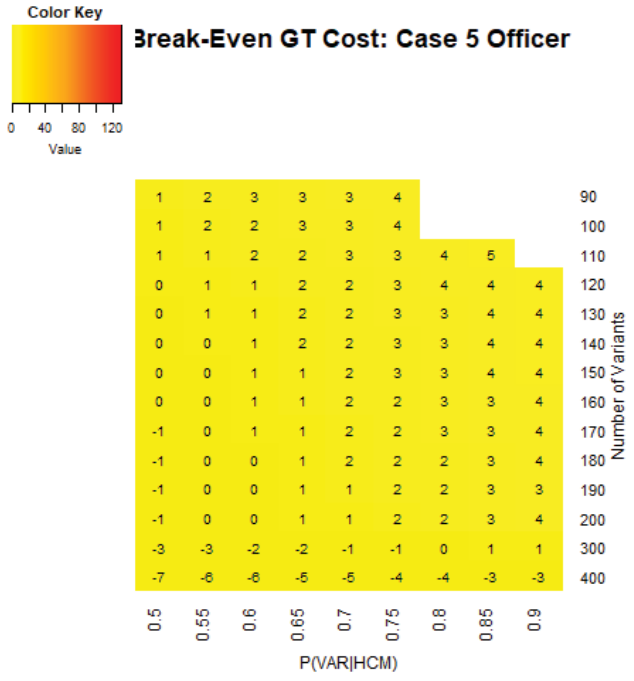


Figure 75: "Break-Even" genetic test costs for Enlisted Case 5.

10.3.3 Enlisted Case 6

In Figure 76, three heatmaps for the cheapest GT costs for enlisted Case 6 are displayed. From these heatmaps, it can be seen that the enlisted Case 6 confers benefit at a smaller GT cost than officer Case 6 did.

Figure 77a displays how the Net benefit changes with changing $\#\ of\ variants$. The slopes of the line appears to be zero, indicating that benefit remains the same as the $\#\ of\ variants$ increases, likely due to the absence of follow-up echocardiograms. In Figure 77b, the Net benefit appears to increase for a greater $P(VAR|HCM)$, likely due to more individuals with HCM being identified by the test.

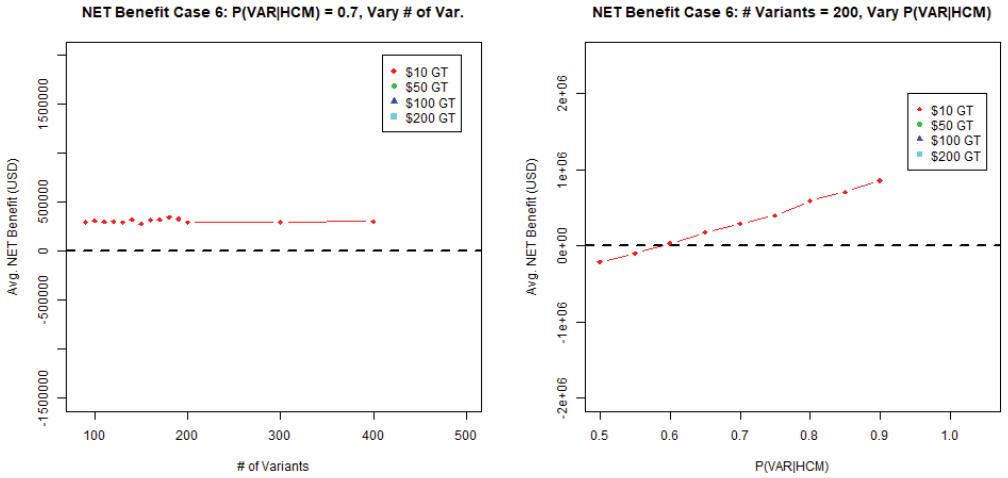
In Figure 78, the "break-even" genetic test cost values for enlisted Case 6 are displayed. Note that these are smaller than officer cases 3, 5 and 6, but are larger than any other enlisted case.

(a) \$10 Genetic Test
σ : {4e5, 5e5, 5e5, 6e5, 6e5}

(b) \$50 Genetic Test
σ : {4e5, 5e5, 5e5, 6e5, 6e5}

(c) \$100 Genetic Test
σ : {4e5, 5e5, 5e5, 6e5, 6e5}

Figure 76: Heatmaps of the average Net benefit for enlisted Case 6. Standard deviation summary given as: σ: {min, 25th quantile, median, 75th quantile, maximum}.



(a) Vary $\#\ of\ varaints$ (b) Vary $P(VAR|HCM)$

Figure 77: Change in Net Benefit for enlisted Case 6 with either changing $\#\ of\ variants$ or $P(VAR|HCM)$. Note how the Net benefit for enlisted Case 6 appears to remain constant for changing $\#\ of\ variants$, but increases with increasing $P(VAR|HCM)$.

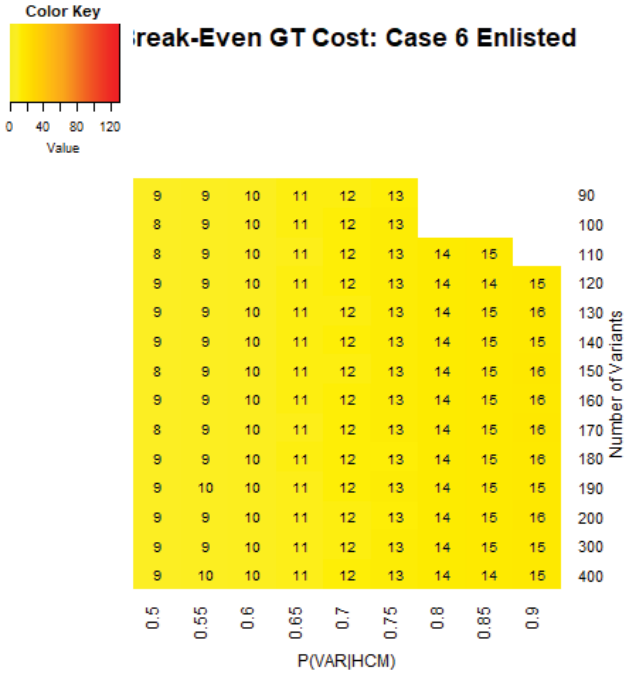
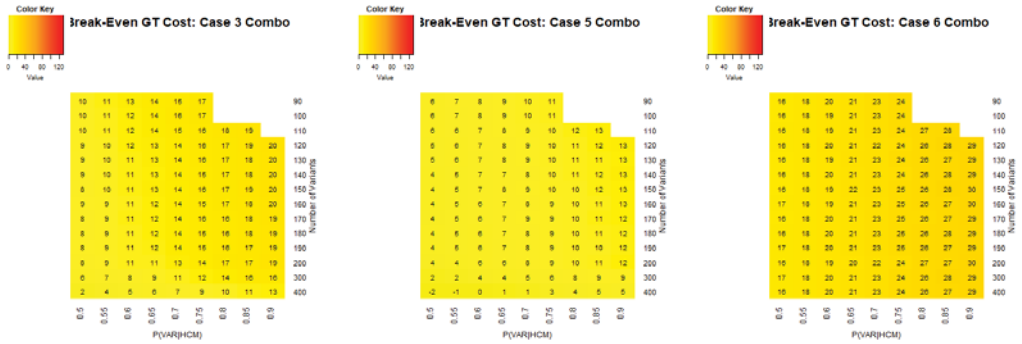


Figure 78: "Break-Even" genetic test costs for Enlisted Case 6.

10.4 Combining Officer and Enlisted Simulations



(a) Case 3 (b) Case 5 (c) Case 6

Figure 79: Heatmaps of where the average value for "Break-even" cost of a genetic test when Net benefit = 0 for a combined officer and enlisted simulation. Note that, in general, these are much lower than from the officer simulation, and slightly higher than the enlisted simulation.

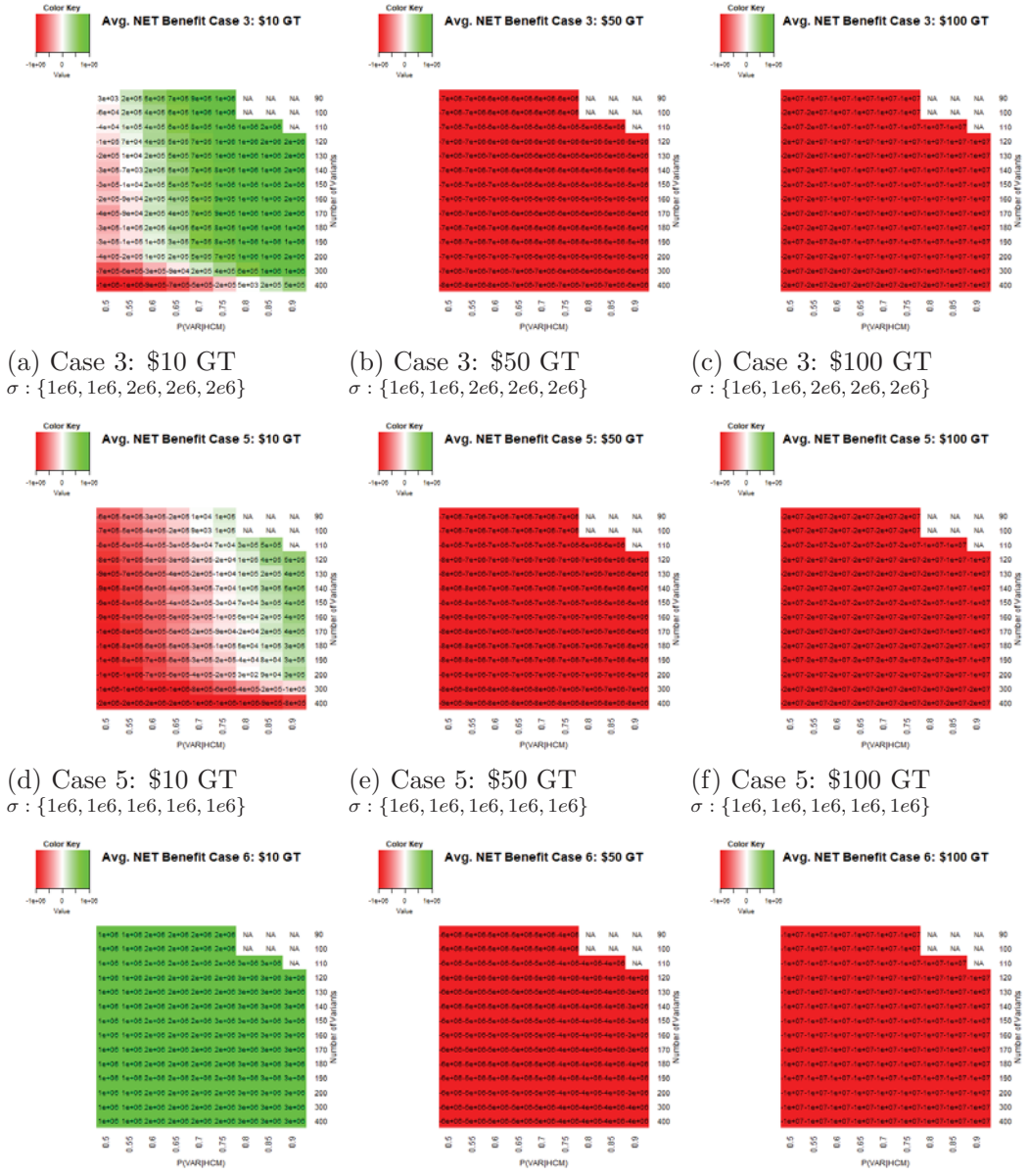
From the previous analysis, it was illustrated that officer screening is much more cost-effective than enlisted screening due to the larger cost of an officer death and the larger time officers spend in the military than enlisted. For previous parameters, such as sensitivity, specificity, FOR, and FDR, the officer and enlisted numbers remained nearly identical, and for measures such as the number of deaths, officer and enlisted simulations may simply be added to obtain the result. For Net benefit, officer and enlisted Net benefit merely needs to be added in order to determine the combined Net benefit. We provide a short analysis of how this addition affects the Net benefit.

Figure 80 displays the average Net benefit for the combined officer and enlisted simulations for each value of $P(VAR|HCM)$ and $\#\ of\ variants$ combination for a \$10, \$50 and \$100 GT. The three genetic cases are shown. Notice how these Net benefits are much lower than they are in the officer simulation, and a positive Net benefit does not occur until around \$10 per genetic test, whereas it occurred at around \$100 per genetic test in the officer simulation. The Net benefits, however, are larger than the enlisted simulation Net benefits. The officer and enlisted simulations somewhat offset each other, however because of the greater enlisted population than the officer population, the Net benefit of the enlisted simulation does not rise as much as the Net benefit of the officer simulation falls. We see the same pattern in Figure 79, which shows the "break-even" genetic test cost for these combined simulations, which is well below \$100 for all genetic tests.

We also see the same trends as previous: for a higher $P(VAR|HCM)$, cases 3, 5 and 6 improve in Net benefit. For a lower $\#\ of\ variants$ value,cases 3 and 5 improve in Net benefit, however the Net benefit of Case 6 remains constant. Because of this, maximizing $P(VAR|HCM)$ and minimizing $\#\ of\ variants$ would be important considerations before utilizing a combined genetic test.

The military, then, must take into account the possibility that genetic screening on only the officer population may be the only cost-effective option. Screening the combined enlisted and officer populations may be cost-effective if the costs associated with genetic

testing are approximatley \$20-\$30, and a high $P(VAR|HCM)$ and low $\#\ of\ variants$ value is obtained.



(a) Case 3: \$10 GT
σ : {1e6, 1e6, 2e6, 2e6, 2e6}

(b) Case 3: \$50 GT
σ : {1e6, 1e6, 2e6, 2e6, 2e6}

(c) Case 3: \$100 GT
σ : {1e6, 1e6, 2e6, 2e6, 2e6}

(d) Case 5: \$10 GT
σ : {1e6, 1e6, 1e6, 1e6, 1e6}

(e) Case 5: \$50 GT
σ : {1e6, 1e6, 1e6, 1e6, 1e6}

(f) Case 5: \$100 GT
σ : {1e6, 1e6, 1e6, 1e6, 1e6}

(g) Case 6: \$10 GT
σ : {1e6, 1e6, 2e6, 2e6, 2e6}

(h) Case 6: \$50 GT
σ : {1e6, 1e6, 2e6, 2e6, 2e6}

(i) Case 6: \$100 GT
σ : {1e6, 1e6, 2e6, 2e6, 2e6}

Figure 80: Heatmaps of the average Net benefit of Cases 3, 5 and 6 for a combined officer and enlisted simulation. Note that, in general, these Net benefits are much lower than the Net benefits from the officer simulation, and slightly higher than the enlisted simulation. Standard deviation summary given as: σ: {min, 25th quantile, median, 75th quantile, maximum}.

11 Variation in the Simulations

It is important to note that in the data analysis, every value used was an average of the 1000 separate populations that were simulated. The reason that averages were used in this simulation is because the military is more likely to be concerned about how the simulation will affect costs and personnel in the long run rather than be concerned about extrema. However, it should be noted that the values presented will not happen for every population, and instead represent an average of values for many populations.

Standard deviations for heatmaps have been presented below the graphs. The standard deviations given represent a range of the standard deviations of each heatmap (given as minimum, 25th quantile, median, 75th quantile, maximum). This means that we took the standard deviations of each of the 119 $P(VAR|HCM)$ and $\#\ of\ variants$ combinations as a set and displayed below the heatmaps the minimum, 25th quantile, median, 75th quantile, maximum. The purpose of this is to give the reader an idea of how the data varied and by how much the data varied.

We illustrate the how variation takes place in the simulation by displaying a density map of the sensitivity of the officer simulation with a $P(VAR|HCM) = 0.5$ and $\#\ of\ variants = 130$ in Figure 81. It can be seen that the simulation has variable sensitivities over the 1000 times it was run.

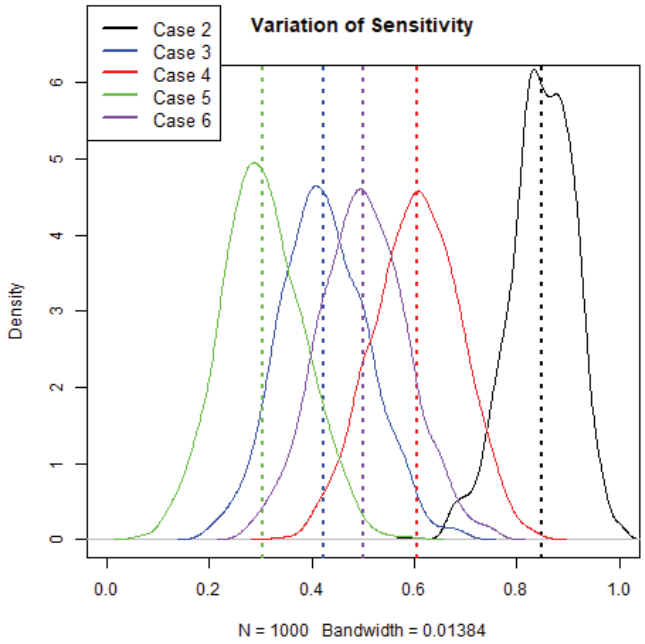


Figure 81: Variation amoung the 1000 officer simulations for sensitivity for a values $P(VAR|HCM) = 0.5$ and $\#\ of\ varaints = 130$. The means of the sensitivities of the cases are displayed as dotted vertical lines. Notice how the sensitivities vary amoung many values for each case, due to random differences in each simulation.

12 Assessing Psychological and Ideological Concerns Through a Survey

We developed a survey to determine the attitudes military members have towards genetic screening. The survey looks to serve as an indicator of the magnitude of resistance to genetic screening and to determine what mechanisms could be performed to allow military members to be more accepting of genetic screening. The survey was developed using questions from two previous studies [45, 46], and additionally by developing new questions. The survey was developed and reviewed with the help of Don Hadley, NHGRI; Pauk Kruszka, NHGRI; Brad Johnson, USNA; and Melonie Teichert, USNA. The survey Questions are provided in Appendix **??**.

12.1 Implementation

The Survey was approved by the United States Naval Academy Human Research Protection Program (HRPP) on 20 April 2018 (Approval # USNA.2018.0030-IR-EM2-A). The survey recruitment email was sent at 9AM on Monday, 23 April 2018. The survey remained open for 48 hours and was closed on 25 April 2018. We provide the form and recruitment email for reference in Appendix D.3.

The survey was distributed via email to all military members of the United States Naval Academy including Midshipmen. 5205 individuals received the recruitment email, and 496 individuals completed the survey (9.5% response rate). All individuals who completed the survey answered all 21 questions.

12.2 Results

12.2.1 Information About Respondents

Basic information about the survey respondents is displayed in Table 16. The disproportionate number of males to females is due to the greater number of males in the military than females.

It is important to note that individuals responded to Question 2 with a number, and we grouped the responses to Question 2 into four distinct categories: individuals who have been in the military for 5 years or less, individuals with military service between 5 and 10 years, individuals with between 10 and 20 years of military service, and individuals with over 20 years of military service. The percentage of individuals in each category is displayed in Table 16.

Additionally, we display in Table 17 the information about individuals' experience with a medical waiver (Q4), genetic disease (Q5), and their knowledge of genetic testing (Q6). In Table 17, percentages are displayed as the fraction of individuals' response out of the total number of respondents, and the 95% confidence interval of the results is displayed below the percents. The confidence intervals are joint confidence intervals calculated based on the multimodal distribution.

Table 16: Information About Survey Respondents

Q1: Have you ever been in the military?				
	Yes	No		
%	99.0	1.0		
Q2: Years of Military Service (include ROTC/service academy)				
	0-5	5-10	10-20	> 20
%	78.9	5.9	7.7	7.5
Q3: Do you have any military service outside of ROTC/Service Academy?				
	Yes	No	N/A	
%	76.2	23.6	0.2	
Q6: Gender				
	Male	Female		
%	64.5	35.5		

Table 17: Experience of Survey Respondents with Military Medicine and Genetics

Q4: Have you been through the process of a medical waiver for any medical condition you have had?			
	Yes	No	Prefer Not to Answer
%	38.7	59.7	1.6
95%CI	$(34.3, 43.2)$	$(55.2, 64.1)$	$(0.0, 6.4)$
Q5: Have you or a family member ever had a medical condition thought to be genetic/inherited?			
	Yes	No	Prefer Not to Answer
%	35.9	61.9	2.2
95%CI	$(31.7, 40.4)$	$(57.7, 66.4)$	$(0.0, 6.7)$

Q7: How much have you read or heard about genetic testing for inherited disease?				
	Almost Nothing	Relatively Little	A Fair Amount	A Lot
%	29.8	49.6	17.9	2.6
95%CI	$(25.2, 34.5)$	$(45.0, 54.3)$	$(13.3, 22.6)$	$(0.0, 7.3)$

12.2.2 Opinions Regarding Genetic Testing

We begin our analysis of the opinions of genetic testing in the military by first analyzing why individuals want to be genetically tested. In Table 18, we display the results from Questions 8 and 9, which ask individuals to rate reasons they would want to be genetically tested; each reason is rated as: "Does Not Apply," "Not At All Important," "Somewhat Important" and "Very Important." Question 9 then asks individuals to pick only one reason as the "Most Important" reason.

From Table 18, it can be seen that the two most important reasons individuals want to

be genetically tested is to both learn about their children's/potential children's risk or to learn about their own risk. Most individuals regarded each reason given in the survey as at least "somewhat important," with "to be reassured" having the least amount of importance among the entire population. From Table 18, we can conclude that individuals want to be genetically tested for a multitude of medical reasons affecting both themselves and others around them.

Table 18: Reasons Individuals Want to Be Genetically Tested (Q8 & Q9)
Q8 responses included in first four conditions. "Most Important" is response to Q9.
All values displayed in Percentages. 95% confidence intervals given below every value.

Reason	Does Not Apply	Not At All Important	Somewhat Important	Very Important	Most Important
To learn about my children's/potential children's risk	6.0 (*2.0, 10.2*)	3.4 (*0.0, 7.6*)	22.4 (*18.3, 26.5*)	68.1 (*64.1, 72.3*)	32.9 (*28.2, 37.6*)
To Learn About My Risk	0.6 (*0.0, 5.1*)	3.2 (*0.0, 7.8*)	34.3 (*30.0, 38.8*)	61.9 (*57.7, 66.4*)	32.7 (*28.0, 37.4*)
To make important medical decisions	1.6 (*0.0, 6.1*)	7.7 (*3.2, 12.2*)	32.5 (*28.0, 37.0*)	58.3 (*53.8, 62.8*)	19.8 (*15.1, 24.4*)
To know if I need to get screening tests more often	1.0 (*0.0, 5.7*)	9.3 (*4.6, 13.9*)	42.1 (*37.5, 46.8*)	47.6 (*42.9, 52.3*)	12.5 (*7.9, 17.2*)
To be reassured	1.2 (*0.0, 6.1*)	27.2 (*22.6, 32.1*)	45.6 (*40.9, 50.4*)	26.0 (*21.4, 30.9*)	2.2 (*0.0, 6.9*)

Table 19 displays the results from Questions 10 and 11, which ask respondents the importance of reasons for NOT wanting to be genetically tested in the same manner as Questions 8 and 9. The most important reason for not wanting to be tested was "worried about losing my job" (39.9% rate most important) and the second most important reason was "worried about losing my insurance" (19.6% rate as most important). Concern over the effects the test results may have on an individuals' family was high as well, with 16.7% of respondents listing it as their most important concern.

These results indicate that individuals in the military do have significant concern over the effects genetic screening may have on their professional as well as personal lives. around 60% of individuals show concern that genetic screening may have some kind of professional detrimental outcome: either loss of job or insurance. If genetic screening were to

be implemented in the military, these concerns would have to be addressed. Additionally, it must be noted that the military population may be unique in this regard, since the US military and federal government are the only institutions that can legally discriminate based on the results of a genetic test in both employment and health insurance due to the genetic information nondiscrimination act (GINA).

The concern for the effect the test results may have on an individual's family (over 60% of individuals list effects on family as at least somewhat important) and the concern that individuals may not be able to handle the diagnosis emotionally (approximately 30% of individuals list emotional concerns as somewhat important) highlights the fact that genetic counseling services would likely be a requirement if the military were to implement genetic screening. Genetic counseling services may allow individuals and families come to terms with and understand the results of their genetic test.

The low numbers of individuals that rate "there is nothing that can be done to prevent genetic disease" and "I do not trust modern medicine" as important (30% or less for both) highlight that currently, individuals are aware and concerned about genetic conditions, and that individuals in general trust the health system and medicine to give them the care they require. This means that although there may be ideological barriers and concerns about employment, individuals may be capable of understanding the result of a genetic test if health professionals were able to adequately explain the diagnosis to them and allow them to understand the results.

After we have identified reasons individuals both want to and do not want to receive genetic testing, Questions 12-19 assess individuals' opinions regarding genetic testing and genetic testing in the military. Each of these questions had the possible responses of "strongly agree," "agree," "neutral," "disagree," and "strongly disagree." We combine the "strongly agree" and "agree" responses as "Agree," and the "strongly disagree" and "disagree" responses as "Disagree" to simplify the analysis in this section. Table 20 displays the results of these questions in percentages with 95% confidence intervals.

From Table 20, we can initially see from Question 12 that individuals are generally curious about their disposition to genetic disease: almost 70% of respondents agreed they are curious, and less than 10% disagreed. Additionally, Questions 13 and 14 display that, in general, individuals are open to the idea of genetic testing. over 60% of individuals agreed they would have their newborn child genetically screened to learn which diseases they may develop, and over 90% of individuals said they would want to know if they had a genetic condition that is treatable. These responses indicate that this population is open to the idea of genetic testing and is open to the use of genetic testing as a mechanism to detect and prevent disease.

The difference in the response between Question 14 and Question 15 is striking. From Table 20, it can be seen that the percentage of individuals who want to know they have a genetic condition that is *treatable* is over 90%, but for a condition that is NOT treatable, only approximately 35% of individuals agreed they would like to know if they had it. This highlights that individuals may only want to use genetic screening selectively and view knowing about an untreatable disease as possibly an unnecessary and excessive burden.

Table 19: Reasons Individuals DO NOT Want to Be Genetically Tested (Q10 & Q11)
Q10 responses included in first four conditions. "Most Important" is response to Q11.
All values displayed in Percentages. 95% confidence intervals given below every value.

Reason	Does Not Apply	Not At All Important	Somewhat Important	Very Important	Most Important
I am worried about losing my job	3.6 (0.0, 8.4)	23.6 (19.0, 28.4)	27.8 (23.2, 32.6)	45.0 (40.3, 49.8)	39.9 (35.1, 44.4)
I am worried about losing my insurance	5.4 (0.8, 10.4)	32.2 (27.6, 37.2)	32.1 (27.4, 37.0)	30.2 (25.6, 35.2)	19.6 (15.1, 24.1)
I am concerned about the effect it would have on my family	3.0 (0.0, 7.9)	32.9 (28.2, 37.7)	44.0 (39.3, 48.8)	20.2 (15.5, 25.0)	16.7 (12.3, 21.3)
My chances of having genetic disease are small	9.7 (5.2, 14.5)	48.6 (44.2, 53.4)	35.3 (30.8, 40.1)	6.5 (2.0, 11.3)	9.3 (4.8, 13.8)
I am concerned that I could not handle it emotionally	5.0 (1.0, 9.4)	65.1 (61.1, 69.5)	24.8 (20.8, 29.2)	5.0 (1.0, 9.4)	6.5 (2.0, 11.0)
I believe that there is nothing that can be done to prevent genetic disease	9.7 (5.4, 14.2)	59.7 (55.4, 64.2)	27.2 (23.0, 31.8)	3.4 (0.0, 8.0)	5.2 (0.8, 9.8)
I do not trust modern medicine	11.9 (8.3, 15.7)	74.6 (71.0, 78.4)	11.5 (7.9, 15.3)	2.0 (0.0, 5.8)	2.8 (0.0, 7.3)

Question 16 asks individuals their opinion of genetic testing in the military to make employment decisions. Over 60% of respondents disagreed that this should be done, and less than 15% agreed it should be done. This response highlights that individuals in the military are generally not open to using genetic screening to make employment decisions. This may be due to the fact that individuals in the military do not desire any additional medical screening test that may merit disqualification. Additionally, the responses to Question 17 indicate that individuals in the military are concerned about genetic results not staying confidential, as around 60% of individuals expressed this concern. If the military were to implement genetic testing, they would likely have to assure that they educate

its members on how genetic testing is guaranteed to stay confidential and what safeguards are in place to keep the genetic information safe. These two responses highlight that there is significant concern, and would likely be significant opposition to, genetic screening in the military and the military would likely have to respond with education regarding the testing and handling of results.

Despite the fact that less than 15% of individuals agreed that genetic screening should be implemented in the military, Question 18 gives a scenario in which an individual has already undergone a genetic screening test and is identified as having a substantial sudden cardiac death risk. Nearly half of the respondents agreed the individual should be prevented from piloting aircraft, and only 1/3 of respondents disagreed. Additionally, the responses to Question 18 and to Question 19, which looked to see how individuals respond to a high risk individual identified by a *non-genetic* test, were similar. This indicates that individuals in the military do not necessarily see genetic testing as inherently different than non-genetic testing. In the case of the F/A-18 pilots in Question 18 and 19, the resulting chance of cardiac problems from the tests were the determining factors in the decision to agree or disagree, not the nature of the test itself.

Finally, we discuss the results regarding Questions 20 and 21, which ask respondents to indicate what level of risk to develop genetic disease would make the genetic test useful in general (Question 20), and be useful for making employment decisions in the military (Question 21). Table 21 displays the percentage results and 95% confidence intervals of the results, and Figure 82 visually displays the distribution of responses and differences between the responses between the two questions. the "No GT" response indicates that no genetic test should be implemented in the military or no genetic test would be useful regardless of the certainty of disease it indicates.

From Table 21 and Figure 82, it can be seen that the majority of individuals, when answering Question 20, appear to have values between 25% certainty of disease and 99% certainty of disease where they believe the genetic test may be useful. Generally, individuals seem to respond that a test with a less than 25% certainty of disease is not as useful, and requiring 100% certainty of disease from a genetic test does not appear to be a required standard in general. Additionally, less than 5% of respondents said that no genetic test (No GT) would be useful. This indicates that individuals are willing to accept some uncertainty in a genetic test result, and overall most individuals in the military are open to the idea of genetic testing when it relates to identifying disease.

The responses to Question 21, however, show that military members require higher standards of certainty of genetic tests when employment decisions are being made. This makes sense, since it would be expected that a test should be accurate if it is used to affect an individual's professional career. less individuals accepted lower certainty of disease, and more individuals said that 100% certainty was required. Additionally, a greater amount of individuals responded that no genetic test should be implemented to make employment decisions in the military. These results indicate that individuals in the military may view genetic screening as useful in general and accept some inaccuracy, but do not accept as much inaccuracy and do not accept genetic screening as much if it is used to make employment decisions.

Table 20: Military Opinions on Genetic Testing (Q12-19)
All values displayed in percentages. 95% confidence intervals given below every value.

Question	Agree	Neutral	Disagree
Q12: I am curious about my disposition to develop genetic disease.	68.5 (64.5, 72.7)	23.8 (19.8, 27.9)	7.7 (3.6, 11.8)
Q13: I would have my newborn child genetically tested to learn which diseases they may develop in adulthood.	62.3 (58.1, 66.7)	19.8 (15.5, 24.2)	17.9 (13.7, 22.4)
Q14: I would want to know if I had a genetic condition that is treatable.	92.9 (90.9, 95.1)	6.0 (4.0, 8.2)	1.0 (0.0, 3.1)
Q15: I would want to know if I had a genetic condition that currently has no effective treatment or cure.	35.1 (30.4, 39.9)	17.7 (13.1, 22.5)	47.2 (42.5, 52.0)
Q16: A person identified with genetic risk of disease should be disqualified from military service or reassigned to a different position.	14.3 (10.1, 18.8)	23.8 (19.6, 28.3)	61.9 (57.7, 66.4)
Q17: I am worried that if I were to have genetic testing, the results may not stay confidential.	60.5 (56.2, 65.0)	16.9 (12.7, 21.5)	22.6 (18.3, 27.1)
Q18: A Navy F/A-18 pilot has undergone genetic testing and is found to have a genetic variant with a 40% chance of causing sudden cardiac death over 5 years. This individual should be prevented from piloting aircraft.	45.4 (40.7, 50.2)	21.4 (16.7, 26.2)	33.3 (28.6, 38.1)
Q19: A Navy F/A-18 pilot has undergone routine, non-genetic blood pressure and cholesterol testing. The tests indicate that there is a 40% chance of cardiac arrest over the next 5 years. This individual should be prevented from piloting aircraft.	47.0 (42.3, 51.8)	20.0 (15.3, 24.8)	33.1 (28.4, 37.9)

Table 21: Risk of Disease and Genetic Testing (Q20-21)
All values displayed in percentages. 95% confidence intervals given below every value.

Question	**<25%**	**25%-49%**	**50%-74%**	**75%-99%**	**100%**	**No GT**
Q20	7.9 $(3.4, 12.7)$	21.8 $(17.3, 26.6)$	38.1 $(33.7, 42.9)$	24.8 $(20.4, 29.6)$	3.2 $(0.0, 8.0)$	4.2 $(0.0, 9.1)$
Q21	2.8 $(0.0, 7.4)$	16.5 $(12.1, 21.1)$	22.6 $(18.1, 27.1)$	22.8 $(18.3, 27.3)$	11.3 $(6.9, 15.8)$	24.0 $(19.6, 28.5)$

Q20: In your opinion, what level of risk to develop the disease makes genetic testing useful?
Q21: In your opinion, what level of risk to develop the disease should an individual be considered for military disqualification or reassignment for medical reasons based on a genetic test?

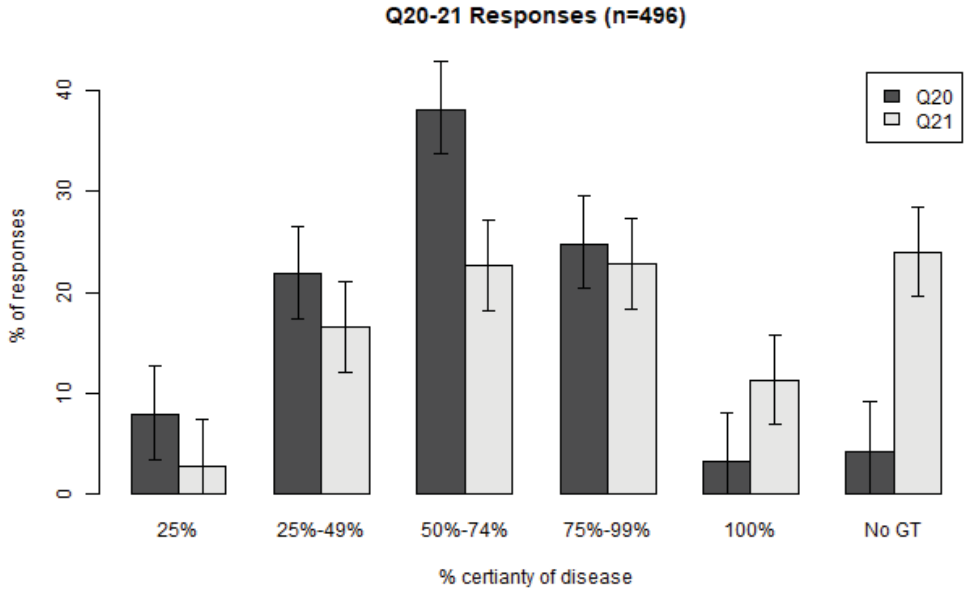


Figure 82: Responses to Questions 20 and 21. Notice how for question 21, which asks what certainty of knowing disease from a genetic test should be required to make military employment decisions, more certainty is required and more individuals say that a genetic test should not be used regardless.

12.2.3 Differences in Responses Among Subgroups

Questions 2-7 were used to identify subgroups of individuals to see if the responses to Questions 8-21 were any way dependent on the responses to Questions 2-7. In this section, we discuss some dependencies which we find interesting and significant. It is important to note that the responses to Question 8 were grouped the same way they were in Table 17, and Questions 12-19 were analyzed with the combined Agree/Neutral/Disagree responses used in Table 20.

Table 22 displays χ^2 p-values of questions we find dependent on another. In the table, an X indicates an insignificant p-value > 0.05. p-values less than 0.05 are displayed. These low p-values indicate that there is some dependency of the response to one question to another. For example, Table 22 indicates there is a dependency on how an individual responded to Question 2 and Question 8a, but no dependency on how an individual responded to Question 2 and Question 8b. Bolded low p-values are discussed in this section. Unbolded p-values show dependency that we do not discuss. All questions are listed in Appendix **??**. The sub-questions among Questions 8 and 10 represent the different possible reasons for wanting/not wanting to be genetically tested. The questions are numbered as they have been previously in this section. Questions 8a-8e and 10a-10g are the responses to the questions asking individuals to rate reasons for wanting (Q8) and not wanting (Q10) to take a genetic test. They are displayed the same order as in the survey form in Appendix D.3.

We first discuss the relationship between Question 2 and Questions 8-21. We found that individuals who have been in the military for a longer period of time were less likely to place importance on their risk for genetic disease (Q8a) as a reason for being tested, and also were less likely to worry about losing their job from the results of a genetic test (Q10f). These results may be explained by the fact that the individuals have progressed farther in their careers and are older, and so are not as concerned about losing their jobs and may be less concerned with genetic disease in general. Additionally, individuals who had spend more time in the military were less likely to trust modern medicine (Q10b) and were also less likely to respond that they would have their children screened for genetic disease (Q13). Individuals who had spent more time in the military were also less likely to agree with preventing an individual from piloting aircraft as a result from both a genetic and non-genetic test (Q18 and Q19).

The relationship between Question 3 (do you have any military service outside ROTC/service academy) and Questions 8-21 parallels somewhat with the relationship between Question 2 and 8-21. Individuals who had service outside of ROTC/service academy were less likely to be concerned about losing their jobs (Q10f), less likely to want to have their children genetically tested (Q13), and less likely to agree that the individual in Q18 and Q19 should be prevented from piloting aircraft. Additionally, individuals who had service outside of ROTC/service academy were *less* concerned about the impact the results of genetic testing may have on their families (Q10a), said their risk of developing genetic disease was smaller (Q11), and were also more concerned about losing their insurance as a result from a genetic test (Q10e) than individuals who have only been at ROTC/service academy. Overall, individuals who have service outside of ROTC/service academy are less likely to be concerned about family effects, job loss, and view thier risk of genetic

Table 22: χ^2 p-values displaying the relationships among the answers to identifying questions (Q2-Q7) and opinions of genetic testing in the military (Q8-Q21). X represents $p > 0.05$. Bolded p-values are discussed in the main text.

Related Question	Q2	Q3	Q4	Q5	Q6	Q7
Q8a	**0.03**	X	0.0003	0.003	0.03	X
Q8b	X	X	X	0.03	X	X
Q8c	X	X	0.02	X	**0.01**	X
Q8d	X	X	0.01	X	**0.0001**	X
Q8e	X	X	0.05	0.02	X	X
Q9	X	X	X	X	X	X
Q10a	X	**0.03**	X	X	X	X
Q10b	**0.02**	X	0.02	X	X	X
Q10c	X	X	X	X	X	X
Q10d	X	X	X	X	**0.005**	X
Q10e	X	**0.04**	X	X	X	X
Q10f	**0.0007**	**0.0001**	X	X	X	X
Q10g	X	X	X	X	X	X
Q11	X	**0.008**	X	0.01	**0.03**	X
Q12	X	X	X	X	**0.04**	X
Q13	**0.006**	**0.03**	X	X	X	X
Q14	X	X	X	X	X	X
Q15	X	X	X	X	X	X
Q16	X	X	**0.03**	X	X	X
Q17	X	X	X	**0.02**	X	X
Q18	**0.05**	**0.0009**	X	X	X	X
Q19	**0.01**	**0.0001**	X	X	X	X
Q20	X	X	X	X	X	X
Q21	X	0.04	X	X	X	X

disease as smaller, whereas individuals who have had only ROTC/service academy experience are more likely to be concerned about family effects, job loss, but are less worried about the loss of insurance.

We found one interesting correlation between individuals that reported having been through the process of a medical waiver (Question 4) and the response to Question 16: whether they believed genetic testing should be implemented in the military. Individuals that have been through the medical waiver process were less likely to agree that genetic testing should be implemented in the military and be used to make employment decisions. We attribute this to the fact that being through the medical waiver process exposes individuals to the fear of being discharged for a medical condition.

Individuals who answered that they had a family member who had a medical condition thought to be genetic/inherited (Q5) were found to more likely agree that they were concerned the results of their genetic test would not stay confidential (Q17). This may be due to the fact that they are more concerned the results of their tests may be used against them.

Several interesting relationships among gender (Q6) and the responses to Questions 8-21 were found. Females were more likely to want to be genetically tested to "learn about my risk" (Q8a) and to "know if I need to get screening tests more often" (Q8c). Additionally, females were more likely to respond that they agreed they were curious about their disposition to develop genetic disease (Q12). A possible reason for this is the increasing awareness for the genetic componet of breast cancer and BRCA1/BRCA2 testing. BRCA1/BRCA2 are two genes known to be risk factors for aggressive breast cancer. When an individual tests positive for certain mutations in BRCA1/BRCA2, it is reccomended they have more screening tests and monitoring for breast cancer [47]. Furthermore, females were more likely to want to undergo genetic testing "to be reassured" (Q8d) and expressed more concern over emotionally handling the results of the genetic test (Q10d).

We found no relationships among the amount an individual said they knew about genetic screening (Question 7) and any of the responses of Questions 8-21. Knowledge about genetic testing does not seem to cause opinions regarding the testing to change, and the results appear to be independent of another.

13 Discussion

13.1 ClinVar Analysis and Predicting Pathogenic Variants

The goal of this study was to determine the feasibility, cost/benefit, impact, and factors impacting implementation of genetic testing in the military. We started this study with an exploration of ClinVar pathogenic variants for all conditions by building a computer program that found all of the pathogenic or likely pathogenic variants without conflicting evidence in ClinVar for a select number of genes deemed by the ACMG as clinically significant, and also projected to impact military service. We took these pathogenic variants and found the frequency of the variants in the gnomAD database. From Table 1, which displays the frequency of the pathogenic variants for each gene and associated condition, we can see much variability in how often these variants occur in the gnomAD population. Some variants (such as SDHD and SDHB) occur very frequently (> 0.01), and some variants (such as MEN1) occur much less frequency (< 0.0001). In total, the frequency of all of these variants in gnomAD was 0.305, indicating that if variants are inherited independently and rarely simultaneously, around 30% of the population would have a pathogenic variant. This variability in pathogenic variant frequency as well as the commonality of pathogenic variants illustrates two principles that make only looking at ClinVar problematic. The first issue is the fact that some diseases are more explored than others, which causes wide variability in the number of pathogenic variants per disease and also causes many pathogenic variants to be not included in the ClinVar list for less explored diseases. Secondly, the fact that pathogenic variants have incomplete penetrance: that having a pathogenic variant does not guarantee disease, makes looking at ClinVar problematic.

Instead of focusing on every condition that could possibly impact military service for the rest of the study, we looked at one, and possibly the most impactful, disease in the military: Hypertrophic Cardiomyopathy. The focus on one disease was to allow us to obtain the most high-quality analysis possible for one condition that could be eventually extrapolated to other conditions. We began this by predicting what variants that cause HCM are not included in ClinVar by creating a logistic regression model built upon variants classified as pathogenic by ClinVar. From this endeavor, we discovered several important findings.

Firstly, from the analysis of the 1000 genomes database outlined in section 7.4, we found that the pathogenic variants in HCM do not appear to be linked: that they are inherited independently of another. This is important for analysis, because the gnomAD frequencies may be treated as the true frequencies in the population, since an individual is not expected to have more than one pathogenic variant.

Predictive model performance with different variables also allowed important findings. In the top five models according to AIC over both MYBC3 and MYH7, all of the models included dbscsnv (splice indicator) and an indicator for an amino acid change. We see through this analysis the importance of these parameters in model selection: that splice indicator and amino acid change indicators are crucial for good model performance. However, it is also interesting to note that these factors perform poorly by themselves. The model with splice indicator by itself was ranked 63/64, and the model with amino acid

change indicator by itself was ranked 53/64. From this, we can see that there is no single parameter that overrules others in importance in model building, and instead it is the correct combination of parameters that allows a model to operate most effectively. Another important finding was that whole-genome algorithms of predicting conservation and deliriousness did not perform as well as custom models with a variety of parameters fitted to two specific genes. CADD, a widely recognized model for predicting pathogenicity of variants, was ranked 37/64 models when placed alone in logistic regression. Although CADD performed better alone than any other single parameter, its performance by itself was not adequate in comparison to other models with combined parameters. From this, it is presumed that the difference in model performance is due to the localized nature of the model: the fact that CADD is fitted to the whole genome, and that the models built in this study are fitted to two specific genes of a specific condition.

Additionally, the difference between how models fit a small amount of data verses a larger set of data can be seen through building the logistic regression models for MYH7 and MYBPC3. The top ranked model for MYH7 included Gerp, splice indicator, and amino acid change; the top ranked model for MYBPC3 included amino acid change, Vertebrate PhyloP, splice indicator, and allele frequency. Even among two genes that cause the same condition, variation can be found in what parameters best predict pathogenicity in the two genes. We choose to not independently assign models to the separate genes, however, and assign a model that generalized over both genes to avoid overfitting. Due to the small dataset in each gene of ClinVar pathogenic variants (44 for MYH7 and 46 for MYBPC3), we wanted to assure that the model we used further in the simulation was generalizable over the data in both genes.

After analyzing the performance of the model, which had a cross-validated sensitivity of 94.4% and a specificity of 99.7% at a probability threshold cutoff of 0.7, we conclude that the model built in this study fits the ClinVar data well. We present this as evidence to suggest that our model can be used to predict pathogenicity of variants. However, there are still many more analyses regarding our model that may be performed to further assess its ability to predict pathogenicity. These further analyses are explained in Section 13.6.1.

After creating a model that had an adequate sensitivity and specificity, our cost/benefit simulation allowed us to determine the result of implementing genetic testing in the military. The model, as a whole, classified more variants than we found were able to possibly be pathogenic. This means that although the model was good at distinguishing between pathogenic and benign ClinVar variants, it likely overclassified new variants as pathogenic that have borderline parameters. However, we account for this by creating the "ranked variant" list, which allows us to only include the "top" pathogenic variants as ranked by the model. Based on this list, and a variety of other simulation settings discussed in Section 8, we are able to compare six cases with different levels and approaches to screening.

13.2 Determination of the Optimal Diagnostic Test

Determination of what is the "best" case to perform genetic screening on military populations is a somewhat subjective determination, and we hope that the results obtained

from this study will be able to guide future individuals to determine the most appropriate way to utilize or not utilize genetic testing. However, we provide evidence to suggest that genetic testing for use in military population-level screening for HCM is a possibility both from a monetary standpoint and from the standpoint of diagnostic value. Additionally, compared to echocardiogram only screening, the genetic tests outperform echocardiograms substantially from a monetary standpoint for all combinations of $P(VAR|HCM)$ and $\#\ of\ variants$, especially for lower genetic test costs. Genetic tests with echocardiogram follow-ups also have higher specificities than echocardiogram-only tests, even when comparing Case 3 (a genetic test followed up by a maximum-accuracy echocardiogram) to Case 4 (a maximum-specificity echocardiogram). The sensitivity of the genetic tests with echocardiogram follow-ups decreases compared to the pure echocardiograms; however the decrease in sensitivity is offset by an increase in specificity.

Overall, we notice several broad trends:

1. **Echocardiogram-only tests do not vary in any measurements with changing P(VAR|HCM) or # of variants.** This result illustrates that varying genetic parameters does not affect a non-genetic test, in this case echocardiography, as expected.

2. **For increasing P(VAR|HCM), the sensitivity, accuracy and Net benefit of the *genetic tests* (cases 3, 5 and 6) increase, and the FOR, FDR and number of deaths decrease.** If the proportion of individuals who have HCM who also have a variant increases, the genetic test will become better at detecting people who have HCM.

3. **For increasing # of variants, the specificity, accuracy, and discharge deathrate of the genetic tests decreases, and the FOR and FDR increase.** The Net benefit also decreases slightly for cases 3 and 5, but not for Case 6. If the number of individuals who have pathogenic variants increases without changing the number of individuals who have a variant and have disease ($P(VAR|HCM)$), more people will be falsely classified as "diseased," and the utility of the genetic test will decrease.

4. **Genetic tests vary more with changing genetic variables the less specific their follow-up tests are.** Case 6, with a non-existent follow-up test, exhibits the largest variation among all of the measurements for changing $P(VAR|HCM)$ and $\#\ of\ varaints$ (the slopes in the graphs are more severe and the curves shift more dramatically). Case 3 varies less than Case 6 for the changing genetic variants which has a follow-up maximum accuracy echocardiogram. Case 5 varies even less than Case 3, with a follow-up maximum specificity echocardiogram.

From the list of broad findings above, we can draw some conclusions about how the most effective screening test may be identified. The most effective treatment will provide adequate detection of HCM to prevent death without overclassifying individuals as diseased. We discuss each case below in relation to the measures we used in the results Sections 9 and 10.

Echocardiogram Only Tests (Cases 2 and 4): Echocardiogram only screenings are both not specific enough and too expensive to currently implement. The maximum accuracy echocardiogram screening (Case 2) overclassifies too many individuals to be deemed

effective. With an average specificity of 85.1%, over 2,000 officers and 20,000 enlisted individuals would be erroneously discharged due to the echocardiogram test. It can be seen in this analysis the importance of having an extremely high specificity in population-level screenings: a change in very small percentages in specificity drastically changes the number of false positives, and in this case, the number of individuals erroneously discharged. Although Case 2 does pick up a fair number of individuals that are diseased, it cannot be considered a realistic option to use for population-level screening due to its low specificity.

Case 4 is a much more specific echocardiogram only test than Case 2. Its specificity is greater than that of Case 2, but is still lower than cases 3 or 5 for every $P(VAR|HCM)$ and $\#\ of\ variants$ combination. Case 4, on average, has approximately 17 officer false positives and 150 enlisted false positives. Although these numbers are smaller than for Case 2, they are not ideal. Additionally, Case 4 has a lower sensitivity than Case 2, picking up on average only approximately 60% of those diseased. With increased specificity that makes the screening option somewhat more probable, a decreased sensitivity occurs as well, and Case 4 is not able to prevent as many deaths as Case 2.

For both of the echocardiogram screenings, at the cost of echocardiogram set in our simulation, both of the screenings are too expensive to implement. The military has on average a negative Net benefit and loses a significant amount of money in our simulation with the use of the echocardiogram only screenings. However, it must be noted that if the echocardiogram were to decrease in price, the screening may become more cost effective.

Genetic Test Followed by Echocardiogram (Cases 3 and 5): Both Cases 3 and 5 may be viable screening tests for the military to implement if the cost of genetic testing is low enough. In comparison to Cases 2 and 4, Cases 3 and 5 have relatively high specificities and do not erroneously discharge individuals, especially with a low $\#\ of\ variants$. Case 3 erroneously discharges between approximately 1 and 10 officers and 1 and 90 enlisted on average depending on the $P(VAR|HCM)$ and $\#\ of\ variants$. Case 5 falsely discharges almost no individuals, and has a specificity greater than 0.999. FDR for both of these cases is extremely low as well (between 0.3 and 0 for Case 3 and approximately 0 for Case 5), indicating that if an individual is flagged as "diseased" in cases 3 or 5, they likely do have HCM. The discharge deathrate for Case 3 ranges from approximately 5% for a high $\#\ of\ variants$, and 9% for a low $\#\ of\ variants$. The discharge deathrate and for Case 5 is constantly around 9%. This indicates that many of the individuals that are discharged by these genetic tests *would have died* had they been in the military.

The sensitivity of Case 3 varies depending on the value of $P(VAR|HCM)$, with an average sensitivity below 0.5 for a $P(VAR|HCM) = 0.5$, and a sensitivity as high as an average of approximately 0.77 for a $P(VAR|HCM) = 0.9$. Additionally, the Net benefit of officer Case 3 becomes positive with a genetic test cost of approximately \$100 (and around \$10 for enlisted and \$20 for combined simulations), varying slightly depending of the value of $P(VAR|HCM)$ and $\#\ of\ variants$. Because of the higher specificity of Case 3, the comparable sensitivity and ability to prevent death, and the perceived benefit when lower-cost genetic tests are implemented, we conclude that Case 3 is a reasonable screening test to use given genetic test costs are low enough.

The sensitivity of Case 5 is lower than that of Case 3, and like Case 3 varies depending

on the value of $P(VAR|HCM)$. However, the specificity of Case 5 is near 100%, and less than one individual per population for both officers an enlisted, on average, is erroneously discharged using Case 5. Case 5 has a lower Net benefit than Case 3 and requires a cheaper genetic test to "break even" than Case 3, but this value is not too drastically lower to be out of range of Case 3. If near complete specificity is desired, Case 5 may be a more viable option than Case 3 to pursue for the military.

Genetic Test Only (Case 6): The potential benefits of Case 6 are highly dependent on the scientific parameters $\#\ of\ variants$ and $P(VAR|HCM)$. Thus, it would require further scientific discovery before responsible implementation. Case 6 varies in all measures more than any other case for changing $P(VAR|HCM)$ and $\#\ of\ variants$ values. When a high $P(VAR|HCM)$ and low $\#\ of\ variants$ are used, Case 6 outperforms nearly all other cases in sensitivity, and possesses close to complete specificity. Case 6 also offers the most Net benefit for a given $P(VAR|HCM)$ and $\#\ of\ variants$ value compared to any other case. However, the danger of implementing Case 6 is that individuals may be discharged from the military without phenotypic proof that they actually have the disease, which presents an ethical issue.

Overall: From the previous analysis, we can conclude that genetic tests followed by echocardiograms outperform echocardiograms alone with regards to cost and specificity, and have comparable sensitivities to echocardiograms alone. However, the performance of genetic tests increases with increased $P(VAR|HCM)$ and decreased $\#\ of\ variants$. Therefore, in order to implement genetic screening, these values should be optimized as well. Paradoxically, the development of genetic knowledge may accumulate much faster if a population-level screening is in place. Despite these concerns, we provide data that allows the military to determine at what point genetic screening may be cost-effectively implemented based on the known $P(VAR|HCM)$, $\#\ of\ variants$, and genetic test cost. The question whether Case 5 or Case 3 is more effective is left to whether the military wishes to virtually eliminate false positives (Case 5), or maximize the number of individuals that have HCM and Net benefit (Case 3). Additionally, the military may choose to be selective in the population that it uses the screenings on. We demonstrate in our simulation that screening officers is much more cost-effective than screening enlisted. Depending on the cost of the genetic test available, the military may decide to only screen officers, or screen both officers and enlisted.

13.3 The Cost of a Genetic Test

Genetic tests currently come in two broad categories: next-generation sequencing where whole-genome or whole-exome sequencing can be performed, and array sequencing, where a limited number of genetic regions in the genome are analyzed for specific variants.

Next Generation sequencing (NGS) is a technique where DNA is sequenced from millions of DNA fragments in parallel. The software "aligns" overlapping DNA fragments together by matching the fragments like a puzzle, providing a substantial "depth" of coverage, where each DNA base pair may be sequenced 50 or more times to provide for the greatest amount of accuracy. Next generation sequencing allows a massive amount of information (a whole genome) to be gathered for a relatively cheap price. Next generation

sequencing has driven the cost of genomic sequencing down from over a 3 billion dollars per genome to close to $1000. It is anticipated that a whole genome may be sequenced for less than $1000 by 2021 [28, 48]. However, the high volume of tests required by the military may cause costs to change.

The other type of genetic test that may be implemented is a DNA microarray. A DNA microarray works by having specific probes that can detect specific variants in specific genes. Although these do not provide infromation for the whole genome, they are currently cheaper than whole genome sequencing and are estimated by the NIH Center for Inherited Disease Research to cost $120-$170 per array [49, 50]. Additionally, the Children's Hospital of Philadelphia lists a microarray analysis for as low as $30 [43]. These costs are close to or even under the "break even" costs associated with the officer simulations and the combined officer and enlisted simulations for cases 3, 5 and 6.

With the decreasing cost of genetic tests, it may not be unrealistic that genetic tests may be obtained for $100 or less. Currently, however, costs of next generation sequencing appear to be higher than the "break even" costs calculated in this analysis. A microarray analysis, however, has a cost much closer to and may even be able to currently match this break even genetic test cost.

13.4 Survey Analysis

We provide here discussion of the results from our survey analysis about attitudes of genetic screening in a military population. We conclude that individuals in the military are not inherently opposed to genetic screening, but have concerns regarding its use to determine employment and have concerns about its confidentiality.

We found from our survey that most individuals in the military want to be genetically tested to learn about their own and their children's risk of developing genetic disease. We found that most individuals (approximately 70%) are curious about their disposition to develop genetic disease, and an overwhelming majority ($> 90\%$) would want to know if they had a genetic condition that was treatable. From this, we conclude that individuals in the military *are* open to the concept of genetic testing, and have expressed that they would use genetic testing to find disease and disease risk in both themselves and their children.

However, we also see some of the concerns individuals have regarding genetic screening in the military. Approximately 60% of individuals list either losing their job or insurance as their #1 concern regarding genetic screening. Only around 15% of individuals agree that genetic screening should be implemented to make employment decisions in the military. Confidentiality is also a concern, with around 60% of individuals agreeing it would be a concern for them if genetic testing were implemented. Individuals who had spent more time in the military were more likely to be opposed to genetic testing.

Despite this, almost 50% of individuals agreed an individual should be prevented from piloting aircraft given a scenario when their genetic test showed they had substantial risk of sudden cardiac death. Respondents also did not significantly differ in their responses

to the genetic test and the non-genetic test. We present this to show that despite the opposition to genetic testing for employment, when given the results and potential consequences, more individuals choose to use genetic testing to make employment decisions.

We conclude that individuals in the military generally view genetic testing as a useful medical tool, however oppose it being used as a *screening* tool. If the military were to implement genetic testing, it may have to overcome this opposition to the screening test being used. The military may have to educate its members and provide counseling in order to successfully implement genetic testing. Additionally, because most respondents stated that they trusted modern medicine, allowing the medical community to present its case for genetic testing may also further its implementation.

13.5 Ethical Issues Revisited

After our analysis, we revisit some ethical concerns which should be considered regarding genetic screening in the military.

13.5.1 What Makes a Variant Pathogenic?

The American College of Medical Genetics recommends that findings of pathogenic variants in a select number of genes be reported to individuals to allow them to have information to make important medical decisions. However, the ACMG is also concerned about how various testing companies define "pathogenic." With the explosion of genetic infromation and new algorithms used to determine pathogenicity, it is a concern that testing companies and laboratories are being too liberal in their definition of "pathogenic." Karen E. Weck writes in the March 2018 issue of *Genetics In Medicine* [51]:

> We have an ethical imperative in medical genetics not to overclassify the pathogenicity of variants because this has significant potential to cause downstream harm to patients. Otherwise, we run the risk of genomic sequencing being perceived as a flawed technique with limited clinical utility. In interpreting the results of gnomic sequencing analysis, sequence variants should therefore be considered "uncertain until proven guilty."

Weck's concern highlights that, in genomic medicine, there must be proof before a variant is classified as "pathogenic." This situation discourages the use of the variants classified by our model as pathogenic but not ClinVar without any other "check." Therefore, at this current time, it would be most appropriate to check variants with a follow-up echocardiogram to assure that individuals are not disqualified from military service based on the result of an unproven genetic test. However, when the predictive power of genomic medicine improves, Case 6 could become a possibility.

13.5.2 Providing Medical Care

If the military provides a genetic test and follow-up echocardiogram and detects HCM in a patient, how much more responsibility do they have towards that patient to assure that they receive proper counseling and follow-up medical care? The military must confront

the fact that HCM and other genetic diseases are lifelong conditions, and the care and patient counseling required for their treatment is substantial. If the diagnosis of HCM is made, the military must determine how much counseling it wants to give patients being discharged about the clinical recommendations regarding HCM such as exercise restrictions, and the possibility of ICD implants and beta-blockers. Additionally, does the military have an obligation to refer patients to outside care providers if a diagnosis of HCM is made? These questions must be addressed before screening can be implemented. Additionally, providing counseling and treatment services would cost the military additional money.

13.5.3 The Permanent Consequences of A Marked Genome

Genetic testing is unique in that it analyzes one of the few things that, at least currently, is completely unique to an individual and static throughout an individual's life. Discovering a pathogenic variant is a life-changing event, and is even more life-changing if the diagnosis can impact one's ability to pursue a desired career in the military, drastically changes lifestyle, and one may have to begin treatment for a chronic disease. Therefore, diagnosis must be made carefully and not without regard for the personal and psychological effects it may have on individuals. The survey developed in section 12 tries to address some of these questions; however, the hiring of genetic counseling services will likely be required by the military for the implementation of genetic screening to be done ethically.

13.5.4 The Danger Of Spillover into Other Professions

The Genetic Information Nondiscrimination Act (GINA) prohibits any civilian employer from discriminating any employment decision based off of the results of a genetic test. However, due to the unique demands of the military, this law does not apply. There is a possibility that implementation of genetic screening in the military may set a precedent for other workplaces to administer and discriminate based on genetic tests. Therefore, implementation of genetic screening in the military must coincide with careful language, regulations and monitoring of the workforce to assure that it is not perceived as, and does not set a precedent for other industries discriminating based on genetic results.

13.5.5 The Slippery Slope of Genetic Screening for Disease and Desirable Traits

Included in this analysis is genetic screening to identify and prevent the military from allowing individuals to perform military duties with a disease that causes sudden cardiac death. We present in this study a mutually-beneficial scenario: screening will both prevent the military from incurring the cost of death and may save individuals lives by making them aware of their genetic condition. However, it is important to note that due to the breadth of genetics, it may one day become a slippery slope between what is considered a disease and what the military considers as "enhancement" of their population.

Due to the unique nature of military work, it may be mutually detrimental for both the military and for an individual for an individual to participate in military training or join the military. We offer HCM and SCD as an example of this. Additionally, the scenario we offer is one where it may become physically impossible for an individual in the military to perform their duties. However, we note that the military, in theory, could use genetic screening to identify not only individuals who possess genetic disease, but individuals who possess desirable genetic traits. We view this as an ethically treacherous result.

The military finds strength in its diversity and also in its capabilities to transform individuals with a varying set of backgrounds and skill-sets. The military and its transformative nature allows for individuals to propel themselves to success though hard work from a myriad of backgrounds. Implementing genetic screening to remove individuals with "less desirable" traits is a result to be avoided. We propose that the military may avoid this ethically treacherous result by restricting genetic screening to only diagnosable conditions, and additionally only to conditions that may manifest themselves as ones that would make it physically impossible or so physically prohibitive that an individual will be unable to optimally perform their required duties. It would also be the best case if the screened individuals had a mutually beneficial experience: such as the diagnosis of HCM, which could prevent the individual from having sudden cardiac death upon discharge of the military. However, this still leaves some area for interpretation, such as variants such as BRCA1 or BRCA2 which cause an increased risk of aggressive cancer. The military must look carefully at what it considers as genetic disease in order to implement genetic screening ethically.

13.6 Future Work

13.6.1 Validation of Logistic Regression Model

Note that we treat the "top variants" as *truly* pathogenic in the simulation. Thus, verification of the model through new scientific discoveries is critical to validate results.

1. **Use other pathogenic disease databasees to determine the effectiveness of the model:** ClinVar is not the only disease database that exists to provide an aggregate of disease associations with variants. The Human Genome Mutation Database (HGMD) is another database that provides information on the pathogenicity of variants. Looking at the results of the model used in comparison to the HGMD data is another way to determine the accuracy, sensitivity and specificity of the model.

2. **Run the model on *all possible* single nucleotide polymorphisms in MYH7 and MYBPC3:** The model may be performed on every single SNP possible in the genes MYH7 and MYBPC3, instead of merely all of the variants present in gnomAD. It would be expected that if the model is run on these variants not included in gnomAD, the result would possess a much *higher* proportion of pathogenic variants to total variants than before, because the variants not present in a large, asymptomatic population are much more likely to be pathogenic (no individuals have the variants in the general popultion, it would be presumed that they are more selected

against and cause disease than variants present in the general population). If, after running the model on all possible variants and a higher $\frac{Pathogenic\ variants}{Total\ variants}$ is found than in gnomAD, the model is more likely to be correct.

3. **Look for new confirmed pathogenic variants that arise:** New pathogenic variants are being found every day. Table S2 displays the variants classified by the model as "pathogenic" in order of their ranking in the model and in ClinVar. As more and more variants are found to be clinically significant, the ability of the model to predict these future variants can be assessed. The more times the model is correct in its prediction, the greater its predictive value can be assumed. Additionally, as mentioned previously, performing genetic testing on a large scale allows clinically signficant findings to become much more avalible: as we know more genotypes and clinical result of those genotypes, we can become more and more capable of predicting the clinical result of future genotypes.

13.6.2 Further Cost-Benefit Analysis

1. **Other Costs:** Our cost-benefit simulation did not take into account capital costs or costs of outsourcing genetic tests vs. performing them in-house. Exploration of these costs may yield different results if they are incorporated.

2. **Detection of More Diseases:** Our logistic regression model and cost-benefit analysis performed a specific analysis on one genetic condition and two genes. The expansion of the analysis to multiple genes may reveal that a greater Net benefit may be obtained, because more individuals with genetic conditions may be found using the costs associated with *the same genetic test.* Future cost-benefit analyses may focus on how a multi-gene and multi-disease panel genetic tests may be implemented in the military. However, with expanded genetic and disease coverage, the analysis must also be concerned with limiting false positives, and the potential for false positives increases the more genes and diseases that are analyzed.

3. **Screening Only on Individuals with Family History of Disease:** Individuals who have family members with HCM or other genetic conditions are at increased risk for developing the disease themselves. Another cost-benefit analysis could identify how the military would benefit if it only screened individuals with a family history of disease. Exploration of this could yield benefits with decreased cost of screening.

13.6.3 Simulation Improvements

We incorporated and compared a wide variety of screening cases and simulation parameters as allowed by the finite timeline of this project. Possible future work includes the incorporation of the following, some of which are designed to update settings based on future scientific discoveries and/or changing costs.

1. **Widen Range of Probability Settings** At the time of running the simulation, we used a range of $P(VAR|HCM)$ and $\#\ of\ variants$ values based on extremes reported in the current literature [5]. If future research reveals that a wider range of values may be possible, then it may be of interest to analyze this wider range.

It is straightforward to implement a wider range, however expanding the range of the simulation would also extend computation time.

2. **Updated Cost Figures:** Cost values are ever-changing. For example, we used the Fiscal Year 2015 average cost billed to medicare in the United States [27] to obtain an average value of cost per echocardiogram. This simulation setting is sure to change in future years, and may be updated in the future to reflect the changes in screening and military costs.

3. **Multiple Follow-up Scans:** The American Heart Association recommends that an individual has a follow-up echocardiogram once a year following discovery of a pathogenic variant [11]. The reason for annual follow-ups is because some individuals with HCM will not display the phenotype detectable via echocardiogram until a certain point in their lives. However, our model simulates a one-time follow up echocardiogram. In order to simulate a series of follow-ups accurately, a more clear understanding of the progression of HCM throughout the life of individuals is required. When this clinical information is incorporated into the medical community, it too could be incorporated in our simulation. However, we estimate that the cost to the military may not be significant, since these follow-up echocardiograms will likely occur on only a small percentage of the population.

4. **Vary the Number of Years Individuals Stay in the Military:** Our simulation uses the average time an individual remains in the military as a way of predicting deaths and costs. However, a future simulation may simulate a military population with some individuals remaining in the military until over 20 years, and others leaving the military earlier than the average time an individual stays. This may change the number of individuals that die of SCD due to HCM.

5. **Simulate Continuous Recruitment:** In our simulation, individuals that were discharged or died were not replaced by new individuals joining the force. In the future, an individual joining the force in a discharged individual's place may change the analysis.

13.6.4 Larger-breadth Survey

Our survey was administered to all military members the US Naval Academy as a prospective study on the attitudes regarding genetic testing in the military. Expanding the survey to the entire military may be useful to confirm its results generalize over the entire military population.

14 Conclusion

From this analysis, we were able to first create a logistic regression model that was able to predict Hypertrophic Cardiomyopathy-inducing variants in the genes MYH7 and MYBPC3, and was also able to demonstrate that a gene-specific or disease-specific classifier is better at predicting pathogenicity than a genome-wide classifier. We also created a cost-benefit analysis that determined the sensitivity, specificity, lives saved, and Net monetary benefit incurred by the military for non-genetic and genetic screening options. Finally, we used a survey to determine the attitudes military members have towards genetic screening in the military.

We conclude that genetic screening followed with an echocardiogram may be a feasible option for the military to implement given the cost of genetic tests is low enough (approximately $100 for officers, $20 for a combined officer and enlisted population, and $10 for an enlisted only population) and the percentage of individuals that have HCM and variants on the pathogenic variant list match those studied by the simulation. With current knowledge and technology, it may take time for the cost of genetic screening to be driven down and for the knowledge available to accurately assess how well genetics can predict HCM. However, paradoxically, implementation of genetic screening may cause these discoveries in genetics to be obtained faster.

The ethical, social and psychological impact of genetic screening cannot be overlooked. Our survey demonstrated that individuals in the military are generally not opposed to genetic screening as a medical test, but have concerns about its implementation as a *screening* test to determine employment, as well as its confidentiality. Before the military potentially implements screening, it must consider the education it may require, the consequences of doing so on an individual basis as well as on a population level and be aware of the precedent they may be setting for other employers to follow.

15 References

[1] H. Varmus F. S. Collins. A new initiative on precision medicine. *N Engl J Med*, 2015.

[2] R. E. Eckart et al. Sudden death in young adults: an autopsy-based series of a population undergoing active surveillance. *J Am Coll Cardiol*, 2011.

[3] S. R. Ommen. Hypertrophic cardiomyopathy. *Curr Probl Cardiol*, 2011.

[4] Ed. C. AL, H. C. Hypertrophic cardiomyopathy. *Genereviews*, 2016.

[5] S.K. Viswanathan et al. Hypertrophic cardiomyopathy clinical phenotype is independent of gene mutation and mutation dosage. *PLoS One*, 2017.

[6] Constantinos O'Mahony et al. A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (hcm risk-scd). *European Heart Journal*, 2014.

[7] Paul Taylor et al. War and sacrifice in the post-9/11 era. Technical report, Pew Reserch Center, 2011.

[8] David Richfield. Sarcomere, June 2007.

[9] Bruce Blaus. Illustration of asymmetric septal hypertorphy in hcm, March 2015.

[10] et al. A.M. Rodday. Electrocardiogram screening for disorders that cause sudden cardiac death in asymptomatic children: A meta-analysis. *Pediatrics*, 2012.

[11] American College of Cardiology Foundation American Heart Association. Guideline for the diagnosis and treatment of hypertrophic cardiomyopathy. Technical report, American Heart Association, 2011.

[12] A. Windhausen. Hypertrophic cardiomyopathy echocardiograms. Echopedia.org.

[13] K. Lykens K. G. Fulda. Ethical issues in predictive genetic testing: a public health perspective. *J Med Ethics*, 2006.

[14] D. W. Hadley P. Kruszka, K. Weiss. Kcnq1 gene variants in large asymptomatic populations: Considerations for genomic screening of military cohorts. *Mil Med*, 2017.

[15] R. E. Eckart et al. Sudden death in young adults: a 25-year review of autopsies in military recruits. *Ann Intern Med*, 2004.

[16] K. Hudson S. Baruch. Civilian and military genetics: nondiscrimination policy in a post-gina world. *Am J Hum Genet*, 2008.

[17] S. Richards et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the american college of medical genetics and genomics and the association for molecular pathology. *Genet Med*, 2015.

[18] MansiG123. Single nucleotide polymorphism, May 2016.

[19] H. LaDuca et al. Exome sequencing covers ¿98generation sequencing panels. *PLoS One*, 2017.

[20] Daniel Horspool. An overview of the (basic) central dogma of molecular biochemistry with all enzymes labeled, November 2008.

[21] M. Lek et al. Analysis of protein-coding genetic variation in 60,706 humans. *Nature*, 2016.

[22] M. J. Landrum et al. Clinvar: improving access to variant interpretations and supporting evidence. *Nucleic Acids Res*, 2017.

[23] R Core Team. *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing, Vienna, Austria, 2014.

[24] M. Liebregts N. S. Anavekar J. Veselka R. M. Cooper, C. E. Raphael. New developments in hypertrophic cardiomyopathy. *Can J Cardiol*, 2017.

[25] Defense Manpower Data Center. Dmdc. Technical report, DoD, 2017.

[26] *DOD Instruction 6130.03: Medical Standards for Appointment, Enlistment, or Induction in the Military Services*.

[27] *Outpatient Charge Data CY 2015, Centers for Medicare and Medicaid Services*.

[28] Deirdre Weymann et al. The cost and cost trajectory of whole-genome analysis guiding treatment of patients with advanced cancers. *Mol Genet Genomic Med.*, 2017.

[29] N. Siva. 1000 genomes project. *Nat Biotechnol*, 2008.

[30] A. Auton et al. A global reference for human genetic variation. *Nature*, 2015.

[31] G. M. Cooper et al. Distribution and intensity of constraint in mammalian genomic sequence. *Genome Res*, 2005.

[32] K. R. Rosenbloom A. Siepel K. S. Pollard, M. J. Hubisz. Detection of nonneutral substitution rates on mammalian phylogenies. *Genome Res*, 2010.

[33] M. Kircher et al. A general framework for estimating the relative pathogenicity of human genetic variants. *Nat Genet*, 2014.

[34] D. Graur T. Dagan, Y. Talmor. Ratios of radical to conservative amino acid replacement are affected by mutational and compositional factors and may not be indicative of positive darwinian selection. *Mol Biol Evol*, 2002.

[35] J. Zhang. Rates of conservative and radical nonsynonymous nucleotide substitutions in mammalian nuclear genes. *J Mol Evol*, 2000.

[36] Eric Boerwinkle Xueqiu Jian and Xiaoming Liu1. In silico prediction of splice-altering single nucleotide variants in the human genome. *Nucleic Acids Res.*, 2014.

[37] Kamil Bartoń. *MuMIn: multi-model inference, R package*. R Foundation for Statistical Computing, Vienna, Austria, 2013.

[38] Paweł P. Dimitrow et al. Sudden death in hypertrophic cardiomyopathy: old risk factors re-assessed in a new model of maximalized follow-up. *European Heart Journal*, 2010.

[39] Illumina. Quality scores for next-generation sequencing. Technical report, Illumina, 2011.

[40] *Death Gratituy, US DoD, http://militarypay.defense.gov/Benefits/Death-Gratuity/.*

[41] Matthew D. Sharra. *U.S. Naval Officer accession sources: promotion probability and evaluation of cost.* PhD thesis, Naval Postgraduate School, 2015.

[42] Carl J. Dahlman. The cost of a military person-year. Technical report, RAND Corporation, 2007.

[43] Childrens Hospital of Phihlidelphia. Pricing details for current cag services. Technical report, CHOP, 2018.

[44] *Aline Quester and Robert Shuford, Population Representation in the Military Services: Fiscal Year 2015 Summary Report.*

[45] D. W. Hadley et al. Perceptions of cancer risks and predictors of colon and endometrial cancer screening in women undergoing genetic testing for lynch syndrome. *J Clin Oncol*, 2008.

[46] D. Chokoshvili et al. Public views on genetics and genetic testing: A survey of the general public in belgium. *Genet Test Mol Biomarkers*, 2017.

[47] S. Palunch-Shimon et al. Prevention and screening in brca mutation carriers and other breast/ovarian hereditary cancer syndromes: Esmo clinical practice guidelines for cancer prevention and screening. *Annals of Oncology*, (Supplement 5), 2016.

[48] Sam Behjati1 and Patrick S. Tarpey. What is next generation sequencing? *Arch Dis Child Educ Pract Ed.*, 2013.

[49] Thomas LaFramboise. Single nucleotide polymorphism arrays: a decade of biological, computational and technological advances. *Nucleic Acids Res.*, 2009.

[50] *NIH Institute Pricing, Center for Inherited Disease Research, Feburary 2018.*

[51] Karen E. Weck. Interpretation of genomic sequencing: variants should be considered uncertian until proven guilty. *Genetics in Medicine*, 2018.

A Appendix: Investigating Interactions

In the body of the paper, we often made references to how certain measures changed relative to a changing $P(VAR|HCM)$ or $\#\ of\ variants$. We held either $P(VAR|HCM)$ or $\#\ of\ variants$ constant, and then varied the other variable for a given measure and a given case. The slope of the resulting lines are known as partial derivatives, where one variable changes and all other variables are held constant. Thus, if we observe the change in a measure, and change the $\#\ of\ variants$ while holding $P(VAR|HCM)$ constant, we find:

$$\frac{\partial measure}{\partial \#\ of\ variants} \tag{22}$$

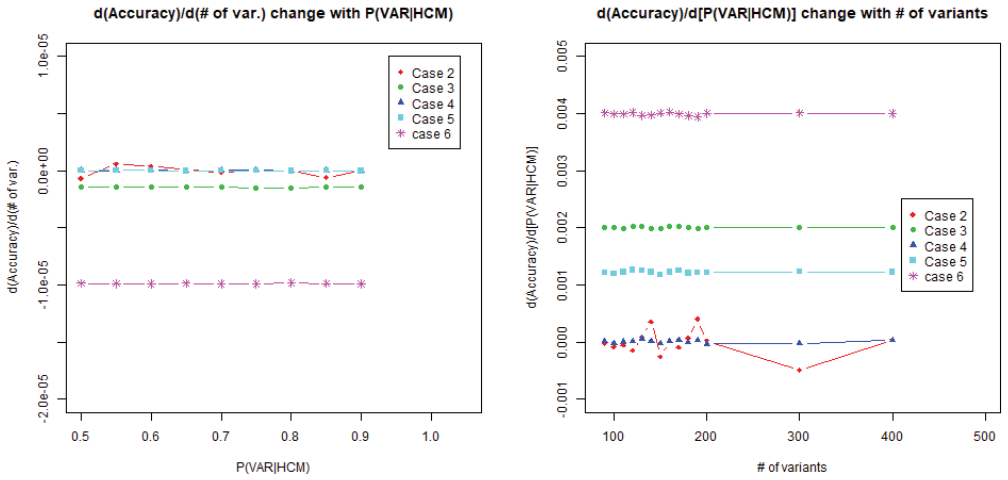
If we observe the change in a measure, and change the $P(VAR|HCM)$ while holding $\#\ of\ variants$ constant, we find:

$$\frac{\partial measure}{\partial P(VAR|HCM)} \tag{23}$$

As stated at the begining of the analysis, it is possible that $\frac{\partial measure}{\partial \#\ of\ variants}$ or $\frac{\partial measure}{\partial P(VAR|HCM)}$ may be different for different values of thier respective constants. For example, a measure may have a positive $\frac{\partial measure}{\partial \#\ of\ variants}$ if the constant value of $P(VAR|HCM)$ is 0.7, but the $\frac{\partial measure}{\partial \#\ of\ variants}$ may decrease if the $P(VAR|HCM)$ is held at 0.9.

In this appendix, we have values for certian measures where we found $\frac{\partial measure}{\partial \#\ of\ variants}$ for each constant value of $P(VAR|HCM)$, and found $\frac{\partial measure}{\partial P(VAR|HCM)}$ for each constant value of $\#\ of\ variants$. The goal of this appendix is to make it more clear the variables interact with each other through exploration of these partial derivatives. Note that we only used the officer simulation for this analysis, however the enlisted simulations returned similar values.

A.1 Accuracy

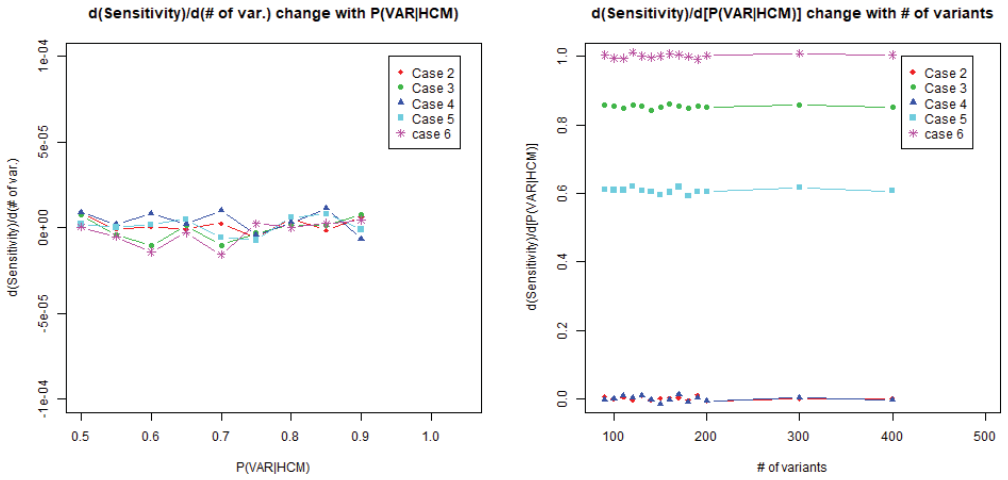


(a) $\frac{\partial Accuracy}{\partial \#\ of\ varaints}$ (b) $\frac{\partial Accuracy}{\partial P(VAR|HCM)}$

Figure S1: $\frac{\partial Accuracy}{\partial \#\ of\ varaints}$ is seen to be most negative for Case 6, followed by Case 3, and zero for cases 2, 4 and 5. $\frac{\partial Accuracy}{\partial P(VAR|HCM)}$ is seen to be most positive for Case 6, followed by Case 3 and zero for cases 2, 4 and 5. All values appear to be constant for the variation of the constants for the partial derivatives.

A.2 Sensitivity

Figure S2 displays the values of $\frac{\partial Sensitivity}{\partial \#\ of\ varaints}$ and $\frac{\partial Sensivitity}{\partial P(VAR|HCM)}$ for each of their respective constants. From Figure S2a, it can be seen that for all values of $P(VAR|HCM)$, $\frac{\partial Sensitivity}{\partial \#\ of\ varaints}$ remains around zero for all cases. Figure S2b displays that a positive constant $\frac{\partial Sensivitity}{\partial P(VAR|HCM)}$ exists for cases 3, 5, and 6 with increasing values from Case 5 to 3 to 6.

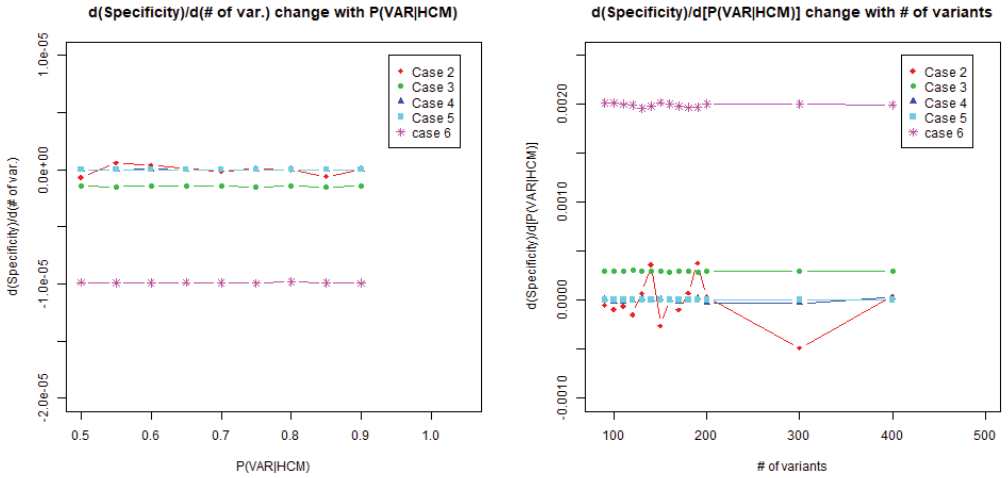


(a) $\frac{\partial Sensitivity}{\partial \#\ of\ varaints}$ (b) $\frac{\partial Sensitivity}{\partial P(VAR|HCM)}$

Figure S2: $\frac{\partial Sensitivity}{P(VAR|HCM)}$ is seen to be most positive for Case 6, followed by Case 3, and zero for cases 2, 4 and 5. $\frac{\partial Sensitivity}{\partial \#\ of\ variants}$ is seen to be approximately zero for all cases. All values appear to be constant for the variation of the constants for the partial derivatives.

A.3 Specificity

Figure S3 displays $\frac{\partial Specificity}{\partial \#\ of\ varaints}$ and $\frac{\partial Specificity}{\partial P(VAR|HCM)}$ as changing with their relative constants. It can be seen in Figure S3a that the most negative $\frac{\partial Specificity}{\partial \#\ of\ varaints}$ occurs with Case 6, followed by Case 3, and cases 5, 4, and 2 have values of $\frac{\partial Specificity}{\partial \#\ of\ varaints}$ of approximately zero. Figure S3b displays that $\frac{\partial Specificity}{\partial P(VAR|HCM)}$ is most positive for Case 6, followed by Case 3, and zero for cases 5, 4, and 2. These trends occur due to the fact that cases 3 and 5 are "checked" by a follow-up echocardiogram, which decreases the likelihood of a false positive, and thus lowers the effect that varying the genetic parameters have on the specificity.

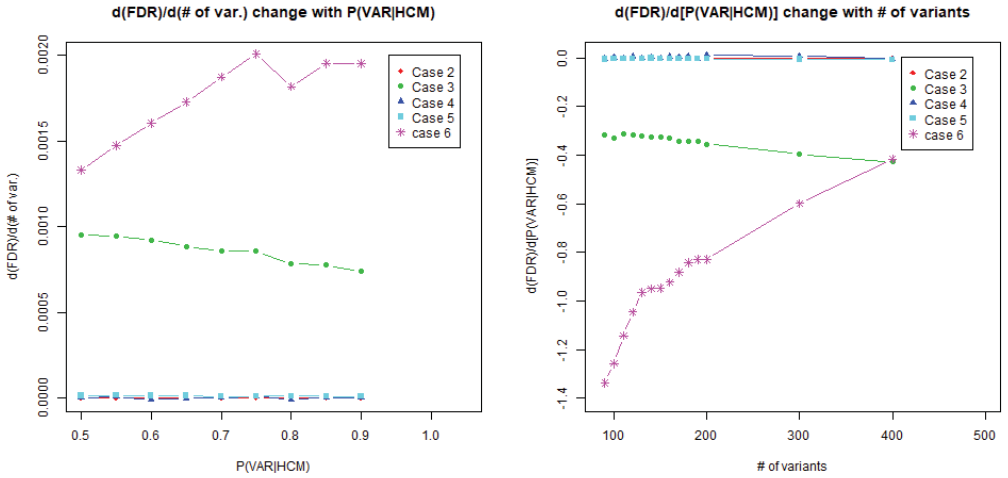


(a) $\frac{\partial Specificity}{\partial \#\ of\ varaints}$ (b) $\frac{\partial Specificity}{\partial P(VAR|HCM)}$

Figure S3: $\frac{\partial Specificity}{\partial \#\ of\ varaints}$ is seen to be most negative for Case 6, followed by Case 3, and zero for cases 2, 4 and 5. $\frac{\partial Specificity}{\partial P(VAR|HCM)}$ is seen to be most positive for Case 6, followed by Case 3 and zero for cases 2, 4 and 5. All values appear to be constant for variation of the respective constants.

A.4 False Discovery Rate

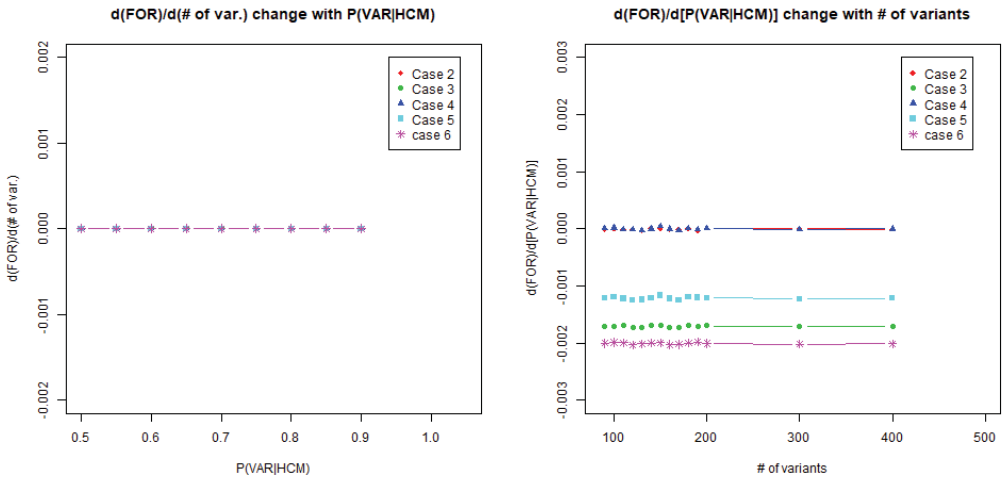
Figure S4 brings an interesting result. Previously, in analysis, $\frac{\partial measure}{\partial \#\ of\ varaints}$ and $\frac{\partial measure}{\partial P(VAR|HCM)}$ remained constant for changing constants associated with the partial derivatives. However, in this case, both $\frac{\partial FDR}{\partial \#\ of\ varaints}$ and $\frac{\partial FDR}{\partial P(VAR|HCM)}$ change for cases 3 and 6 with changing constants. For Case 6, $\frac{\partial FDR}{\partial \#\ of\ varaints}$ increases steadily at first before leveling off for increasing $P(VAR|HCM)$. This indicates that these variables interact with another.



(a) $\frac{\partial FDR}{\partial \#\ of\ varaints}$ (b) $\frac{\partial FDR}{\partial P(VAR|HCM)}$

Figure S4: Notice how these partial derivatives are not constant for their respective constants. Overall, though, $\frac{\partial FDR}{\partial P(VAR|HCM)}$ is negative for genetic tests, and $\frac{\partial FDR}{\partial \#\ of\ varaints}$ is positive for genetic tests. Case 6 appears to vary in its partial derivatives the most an generally increase, and Case 3 appears to generally decrease for both $\frac{\partial FDR}{\partial \#\ of\ varaints}$ and $\frac{\partial FDR}{\partial P(VAR|HCM)}$.

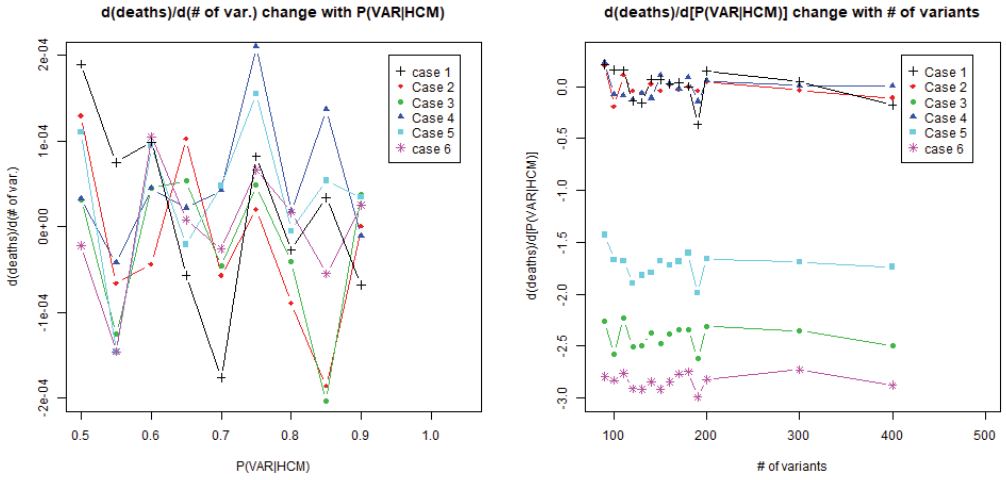
A.5 False Omission Rate



(a) $\frac{\partial FOR}{\partial \#\ of\ varaints}$ (b) $\frac{\partial FOR}{\partial P(VAR|HCM)}$

Figure S5: $\frac{\partial FOR}{\partial \#\ of\ varaints}$ is seen to be most negative for Case 6, followed by Case 3 and Case 5, and zero for cases 2, 4. $\frac{\partial FOR}{\partial P(VAR|HCM)}$ is seen to be approximately zero. All values appear to be constant for the variation of the constants for the partial derivatives.

A.6 Deaths

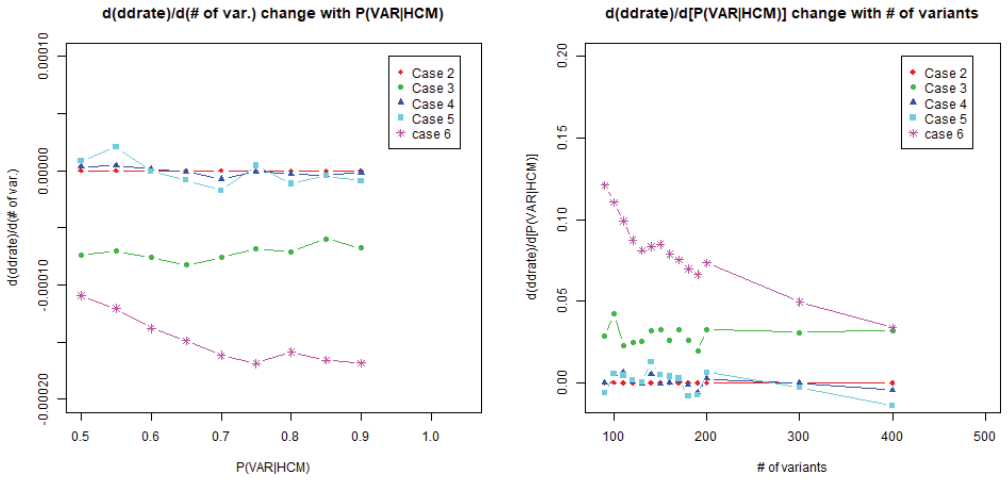


(a) $\frac{\partial deaths}{\partial \#\ of\ varaints}$ (b) $\frac{\partial deaths}{\partial P(VAR|HCM)}$

Figure S6: $\frac{\partial deaths}{\partial \#\ of\ varaints}$ is approximately zero for all cases. $\frac{\partial deaths}{\partial P(VAR|HCM)}$ is most negative for Case 6, followed by Cases 3 and 5. All values appear to be relatively constant with some variation likely due to random error

A.7 Discharge Deathrate

The discharge deathrate, like FDR, does not appear to have constant partial derivatives for all of its constants. Thus, the parameters likely interact. This variation is seen most prominently for Case 6. Overall, $\frac{\partial DDrate}{\partial \#\ of\ varaints}$ is negative for genetic tests, and $\frac{\partial DDrate}{\partial P(VAR|HCM)}$ is positive for genetic tests.



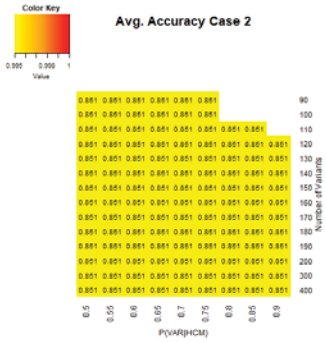
(a) $\frac{\partial DDrate}{\partial \#\ of\ varaints}$ (b) $\frac{\partial DDrate}{\partial P(VAR|HCM)}$

Figure S7: The partial derivatives for discharge deathrate do not have a constant slope, especially for Case 6. Note how $\frac{\partial DDrate}{\partial \#\ of\ varaints}$ is negative for genetic tests, and $\frac{\partial DDrate}{\partial P(VAR|HCM)}$ is positive for genetic tests.

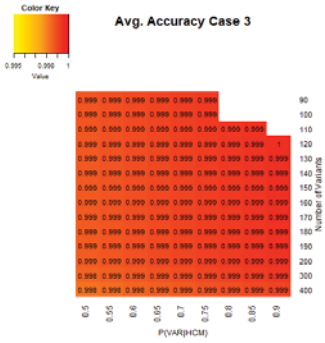
B Appendix: Extra Figures for Enlisted Simulations

We display in this section figures for enlisted simulations that have approximately the same values as in the officer simulations for reference.

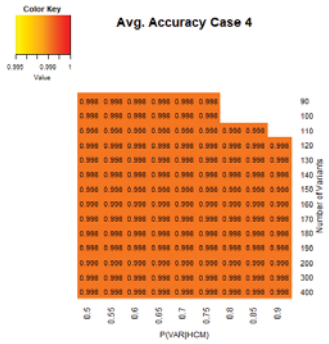
B.1 Accuracy



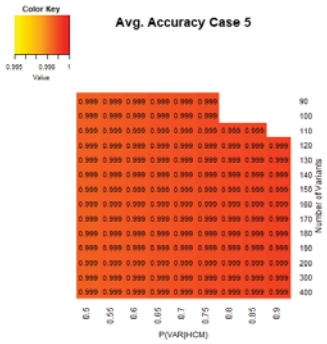
(a) Case 2
σ : {8e-4, 9e-4, 9e-4, 9e-4, 1e-3}



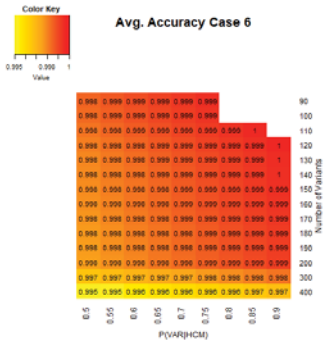
(b) Case 3
σ :{5e-5, 7e-5, 8e-5, 9e-5, 1e-4}



(c) Case 4
σ :{1e-4, 1e-4, 1e-4, 1e-4, 1e-4}

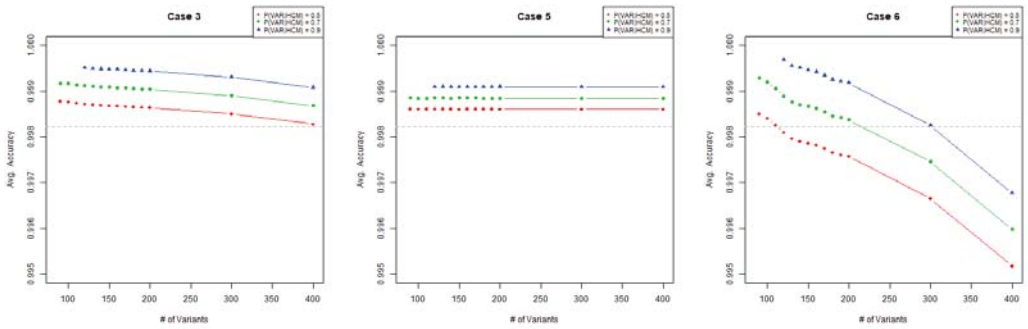


(d) Case 5
σ :{7e-5, 8e-5, 9e-5, 9e-5, 1e-4}



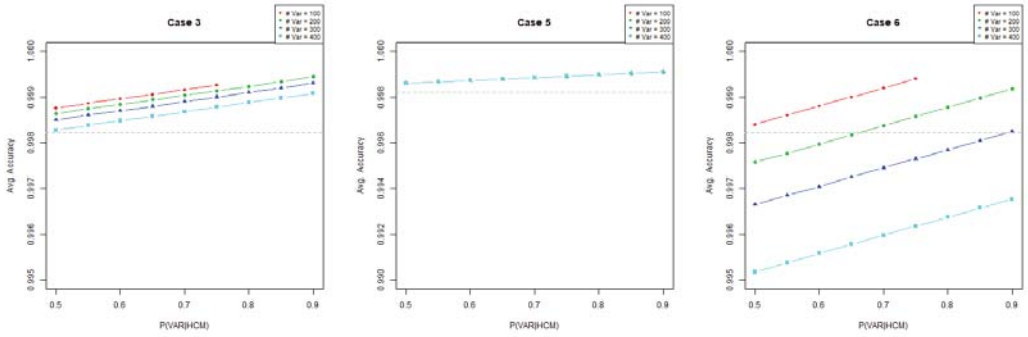
(e) Case 6
σ:{4e-5, 8e-5, 9e-5, 1e-4, 2e-4 }

Figure S8: Heatmaps of the Accuracy for each enlisted case. Standard deviation summary given as $\sigma : \{min,\ 25^{th}\ quantile,\ median,\ 75^{th}\ quantile,\ maximum\}$



(a) Case 3 (b) Case 5 (c) Case 6

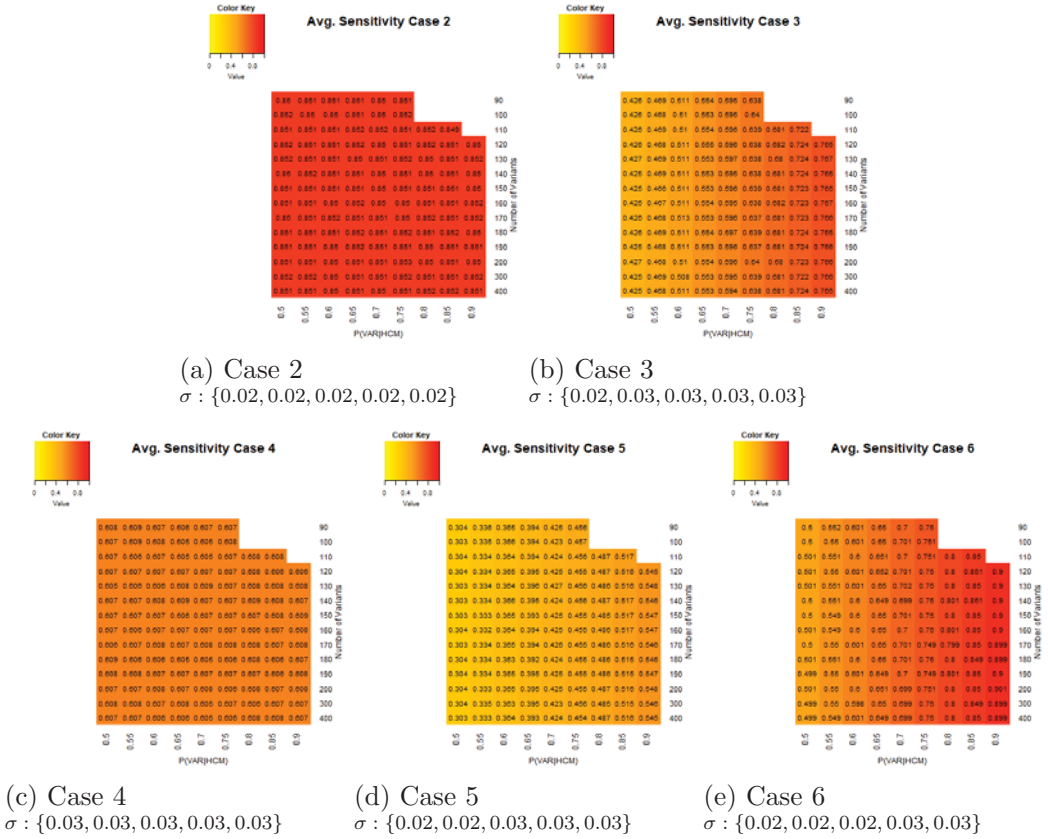
Figure S9: Accuracy, where the *# of variants* were changed for three different constant values of $P(VAR|HCM)$. Notice that the slope of each line is negative, with the largest negative slope with Case 6, followed by Cases 3 and 5, with the y-intercepts of the lines increasing as the constant value for $P(VAR|HCM)$ increases. The lower grey line at approximately 0.6 indicates the average Accuracy of Case 4. Note how the enlisted simulations have approximatley the same values as the officer simulations.



(a) Case 3 (b) Case 5 (c) Case 6

Figure S10: Accuracy, where the $P(VAR|HCM)$ values were changed for four different *# of variants* constants. Lines did not change whatsoever for different *# of variants* constants. Notice the positive slope for all three cases. Note how the slope increases from Case 5 to 3 to 6. The lower grey line at approximately 0.6 indicates the average Accuracy of Case 4. Note how the enlisted simulations have approximately the same values as the officer simulations.

B.2 Sensitivity



(a) Case 2
$\sigma : \{0.02, 0.02, 0.02, 0.02, 0.02\}$

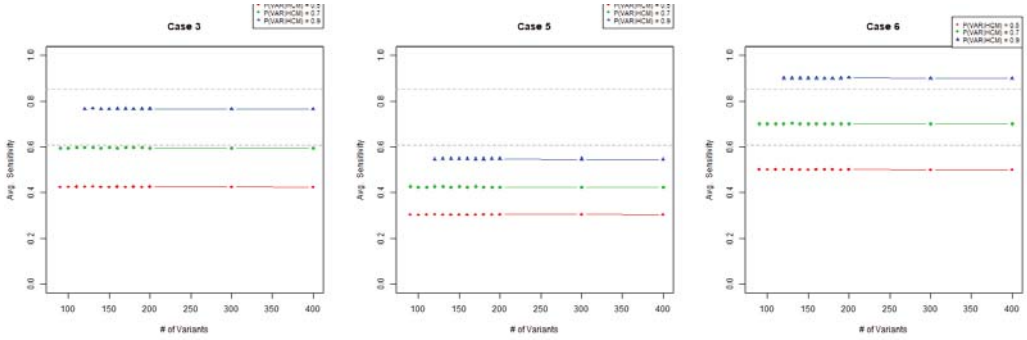
(b) Case 3
$\sigma : \{0.02, 0.03, 0.03, 0.03, 0.03\}$

(c) Case 4
$\sigma : \{0.03, 0.03, 0.03, 0.03, 0.03\}$

(d) Case 5
$\sigma : \{0.02, 0.02, 0.03, 0.03, 0.03\}$

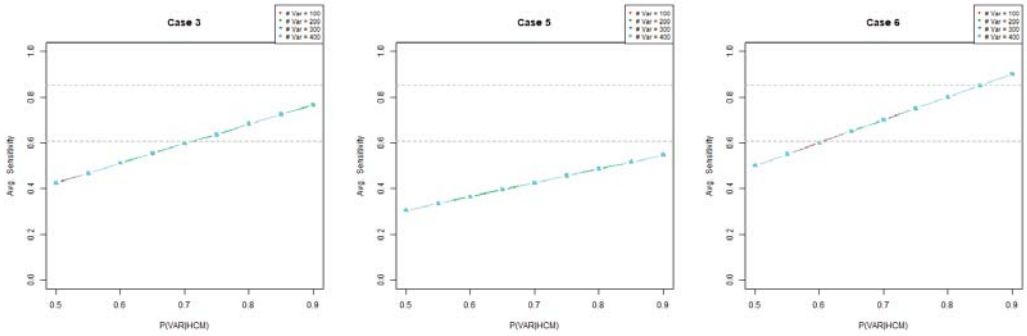
(e) Case 6
$\sigma : \{0.02, 0.02, 0.02, 0.03, 0.03\}$

Figure S11: Heatmaps of the sensitivity for each enlisted case. Standard deviation summary given as $\sigma : \{min,\ 25^{th}\ quantile,\ median,\ 75^{th}\ quantile,\ maximum\}$



(a) Case 3 (b) Case 5 (c) Case 6

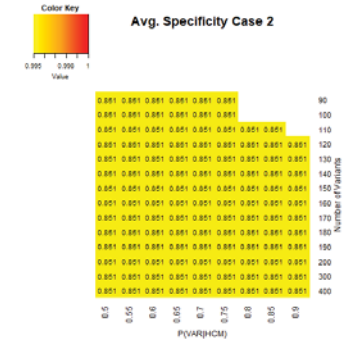
Figure S12: Sensitivity, where the $\#\ of\ variants$ were changed for three different constant values of $P(VAR|HCM)$. Notice that the slope of each line is approximatley zero, with the y-intercepts of the lines increasing as the constant value for $P(VAR|HCM)$ increases. Also note how Case 6 has the highest absolute values for sensitivity for any given $P(VAR|HCM)$, and Case 5 has the lowest. The lower grey line at approximately 0.6 indicates the average sensitivity of Case 4, and the upper grey line at a value of approximately 0.85 indicates the average sensitivity for Case 2.



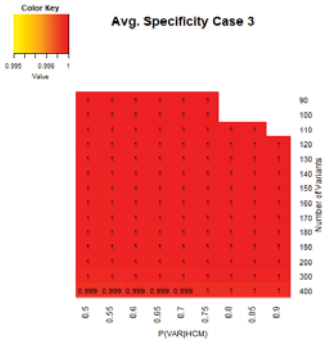
(a) Case 3 (b) Case 5 (c) Case 6

Figure S13: Sensitivity, where the $P(VAR|HCM)$ values were changed for four different $\#\ of\ variants$ constants. Lines did not change whatsoever for different $\#\ of\ variants$ constants. Notice the positive slope for all three cases. Note how the slope and y-intercept increases from Case 5 to 3 to 6. The lower grey line at approximately 0.6 indicates the average sensitivity of Case 4, and the upper grey line at a value of approximately 0.85 indicates the average sensitivity for Case 2.

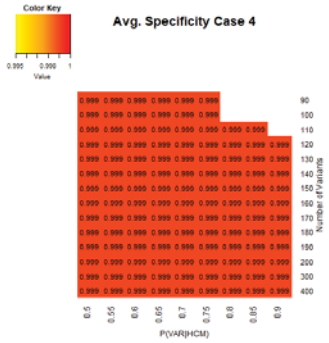
B.3 Specificity



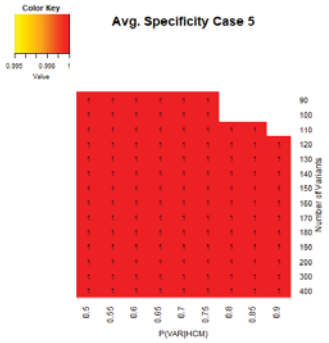
(a) Case 2
$\sigma : \{8e{-}4, 9e{-}4, 9e{-}4, 9e{-}4, 1e{-}3\}$



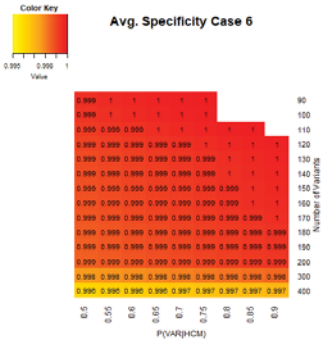
(b) Case 3
$\sigma : \{2e{-}6, 2e{-}5, 3e{-}5, 3e{-}5, 6e{-}5\}$



(c) Case 4
$\sigma : \{8e{-}5, 8e{-}5, 8e{-}5, 8e{-}5, 9e{-}5\}$

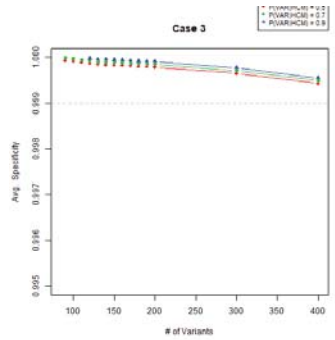


(d) Case 5
$\sigma : \{2e{-}7, 2e{-}6, 3e{-}6, 3e{-}6, 5e{-}6\}$

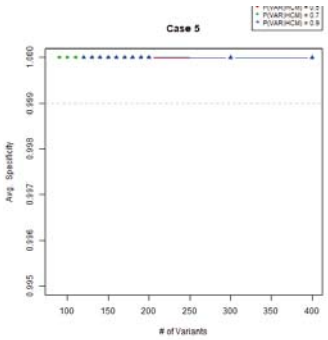


(e) Case 6
$\sigma : \{4e{-}6, 6e{-}5, 7e{-}5, 8e{-}5, 2e{-}4\}$

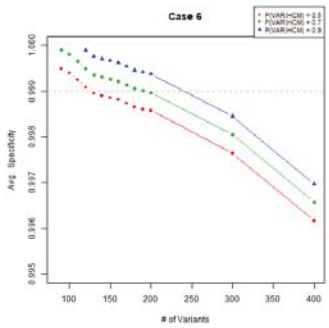
Figure S14: Heatmaps of the average Specificity for each enlisted case. Standard deviation summary given as: σ: {min, 25th quantile, median, 75th quantile, maximum}.



(a) Case 3

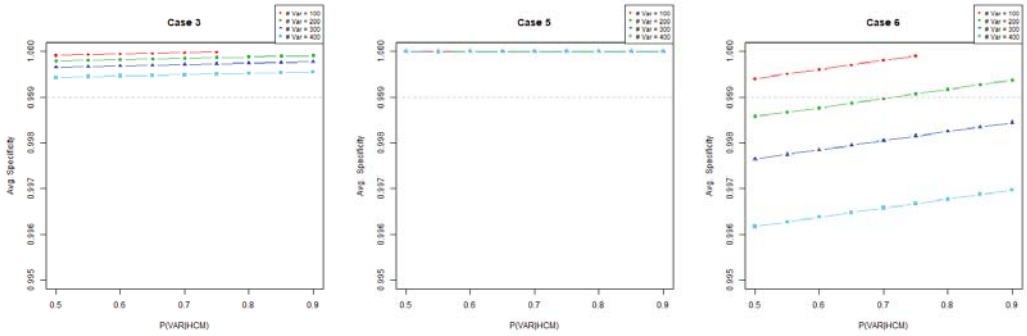


(b) Case 5



(c) Case 6

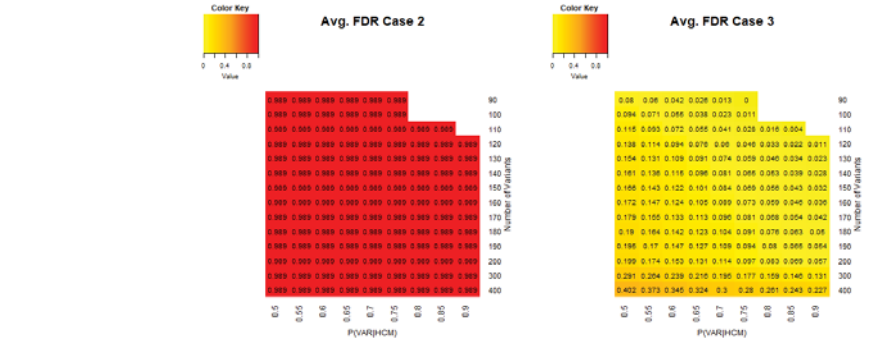
Figure S15: Specificity, where the *# of variants* were changed for three different constant values of $P(VAR|HCM)$. Notice that the slopes of the lines for Case 6 are the most negative, and the slopes of the lines for Case 3 have smaller magnitudes, while Case 5 has flat lines. Increasing $P(VAR|HCM)$ shifts the curves up. Dotted grey line is the average value of specificity for Case 4.



(a) Case 3 (b) Case 5 (c) Case 6

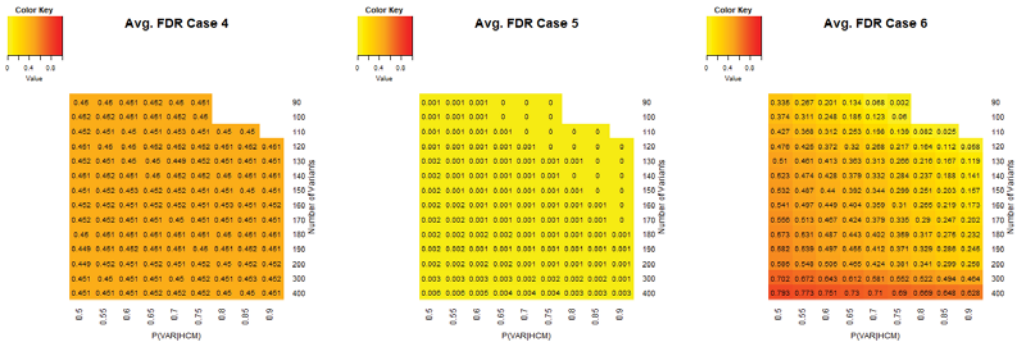
Figure S16: Specificity, where the $P(VAR|HCM)$ was changed for four different constant values of $\#\ of\ variants$. Cases 3 and 6 have positive slopes, with Case 6 having a greater slope and more variation in intercepts for different values of $\#\ of\ variants$. Case 5 has flat lines at approximately 1. The dotted grey line represents the average value for the specificity of Case 4.

B.4 False Discovery Rate



(a) Case 2 $\sigma : \{6e{-}4, 7e{-}4, 7e{-}4, 7e{-}4, 7e{-}4\}$

(b) Case 3 $\sigma : \{2e-3, 0.02, 0.02, 0.03, 0.03\}$

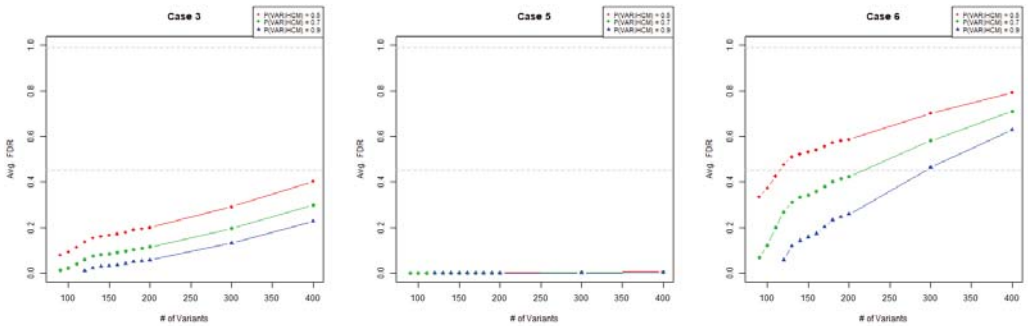


(c) Case 4 $\sigma : \{0.03, 0.030.030.030.03\}$

(d) Case 5 $\sigma : \{2e{-}4, 1e{-}3, 2e{-}3, 3e{-}3, 8e{-}3\}$

(e) Case 6 $\sigma : \{2e-3, 0.02, 0.03, 0.03, 0.03\}$

Figure S17: Heatmaps of the average FDR for each enlisted case. Standard deviation summary given as: σ: {min, 25th quantile, median, 75th quantile, maximum}.

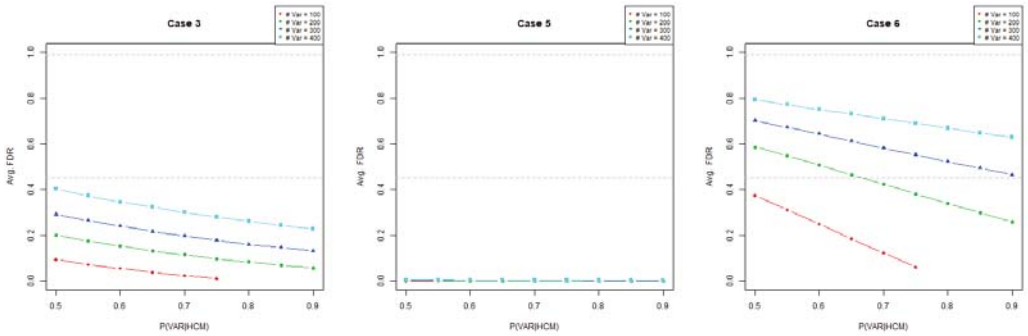


(a) Case 3

(b) Case 5

(c) Case 6

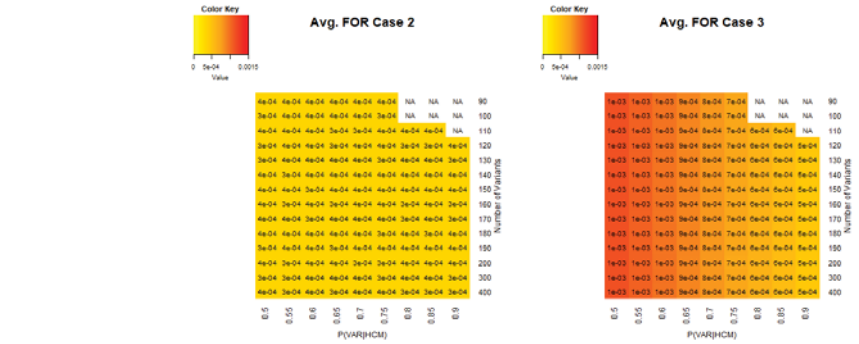
Figure S18: FDR, where the *# of variants* were changed for three different constant values of $P(VAR|HCM)$. Notice that the slopes of the lines for Case 6 are the most positive, and the slopes of the lines for Case 3 have smaller magnitudes, while Case 5 has nearly flat lines. Increasing $P(VAR|HCM)$ shifts the curves up. Also note the somewhat logistical behavior of the Case 6 line. Lower Dotted grey line is the average value of FDR for Case 4, upper dotted grey line is the average value of FDR for Case 2.



(a) Case 3 (b) Case 5 (c) Case 6

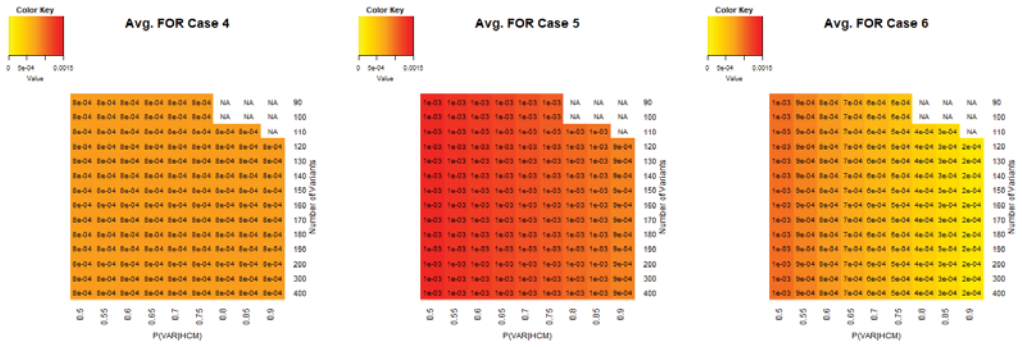
Figure S19: FDR, where the $P(VAR|HCM)$ was changed for four different constant values of $\#\ of\ variants$. Cases 3 and 6 have negative slopes, with Case 6 having a greater slope and more variation in intercepts for different values of $\#\ of\ variants$. Case 5 has flat lines at approximately 0. The lower dotted grey line represents the average value for the FDR of Case 4, the upper dotted grey line represents the average value for the FDR of Case 2.

B.5 False Omission Rate



(a) Case 2 $\sigma : \{5e{-}5, 5e{-}5, 5e{-}5, 5e{-}5, 5e{-}5\}$

(b) Case 3 $\sigma : \{5e{-}5, 7e{-}5, 7e{-}5, 8e{-}5, 9e{-}5\}$

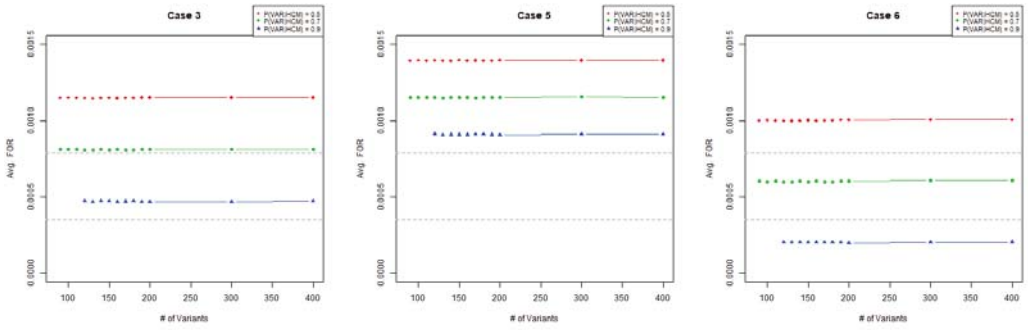


(c) Case 4 $\sigma : \{7e{-}5, 7e{-}5, 7e{-}5, 7e{-}5, 8e{-}5\}$

(d) Case 5 $\sigma : \{7e{-}5, 8e{-}5, 9e{-}5, 9e{-}5, 1e{-}4\}$

(e) Case 6 $\sigma : \{3e{-}5, 5e{-}5, 6e{-}5, 7e{-}5, 8e{-}5\}$

Figure S20: Heatmaps of the average FOR for each enlisted case. Standard deviation summary given as: σ: {min, 25th quantile, median, 75th quantile, maximum}.

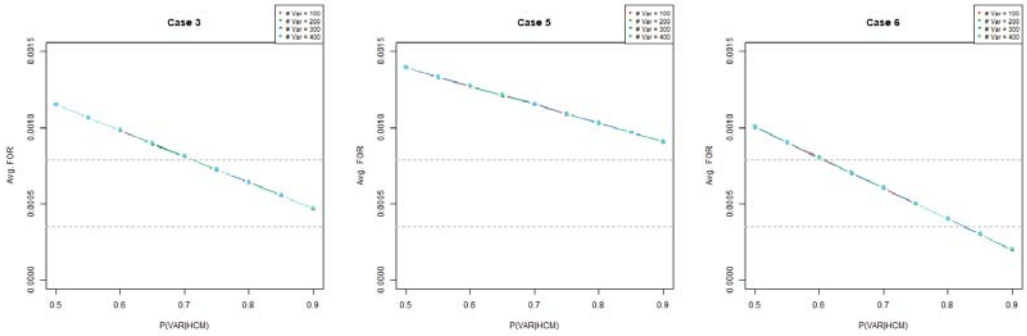


(a) Case 3

(b) Case 5

(c) Case 6

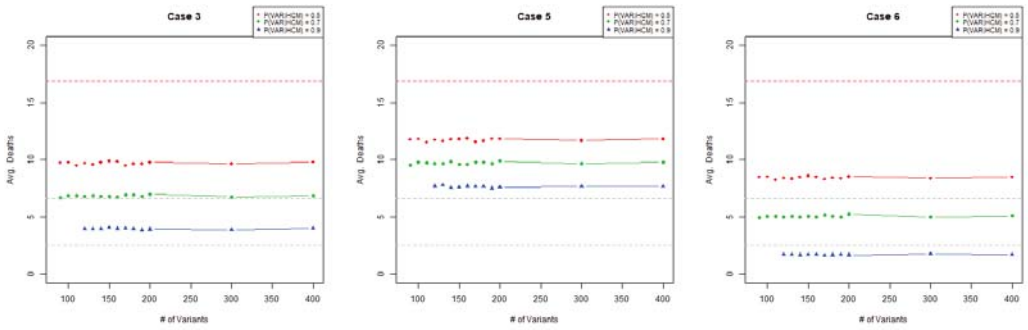
Figure S21: FOR, where the *# of variants* were changed for three different constant values of $P(VAR|HCM)$. Notice that the slopes of the lines are approximately zero. Increasing $P(VAR|HCM)$ shifts the curves up. Lower dotted grey line is the average value of FOR for Case 2, upper dotted grey line is the average value of FOR for Case 4.



(a) Case 3 (b) Case 5 (c) Case 6

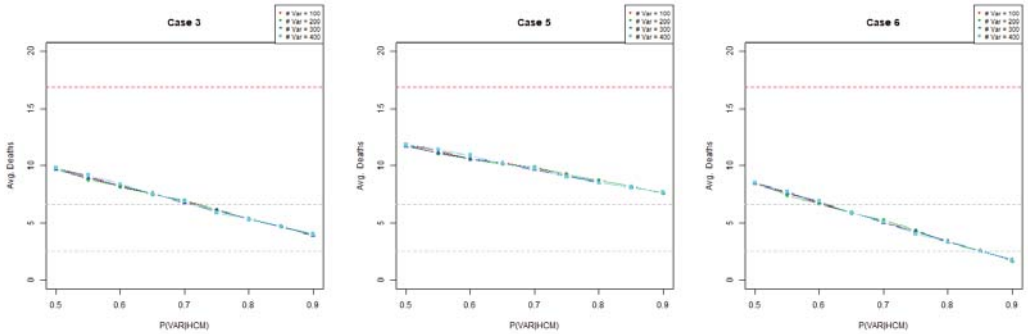
Figure S22: FOR, where the $P(VAR|HCM)$ was changed for four different constant values of $\#\ of\ variants$. Cases 3, 5 and 6 all have negatives slopes, with the largest magnitude of slope of Case 6, followed by cases 3 and then 5. Notice how FOR does not change with changing values of $\#\ of\ variants$. Lower dotted grey line is the average value of FOR for Case 2, upper dotted grey line is the average value of FOR for Case 4.

B.6 Number of Deaths



(a) Case 3 (b) Case 5 (c) Case 6

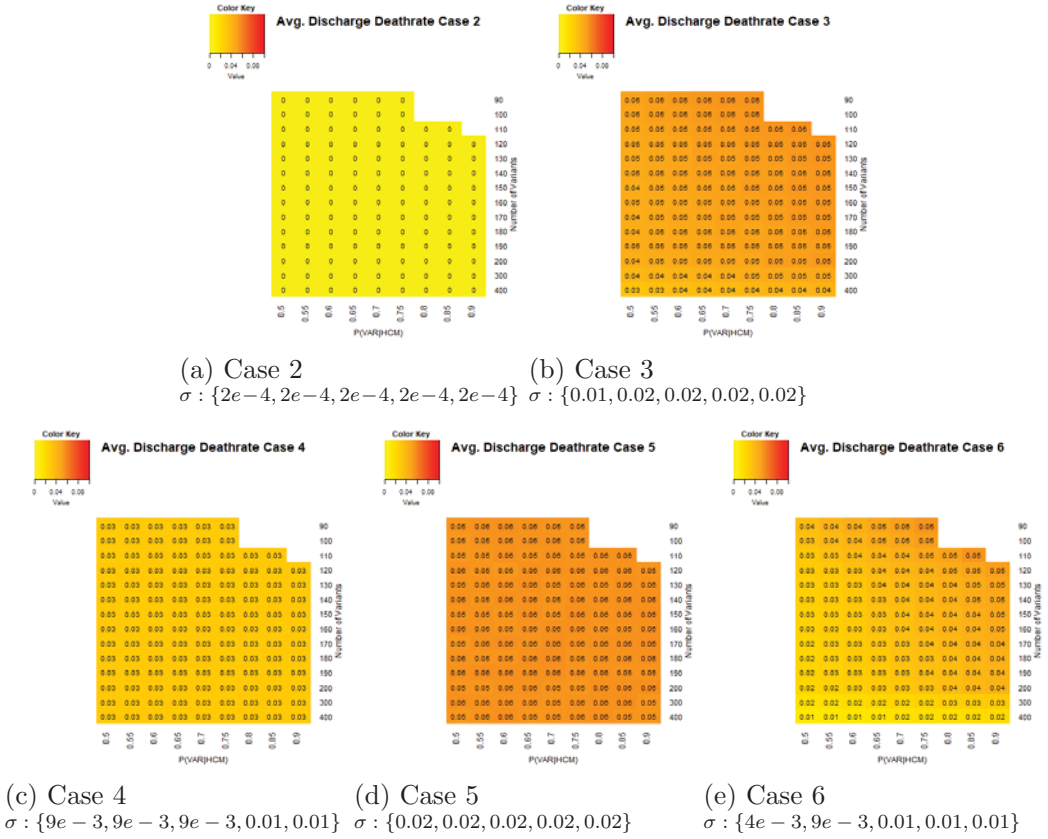
Figure S23: deaths, where the *# of variants* were changed for three different constant values of $P(VAR|HCM)$. Notice how the curves shift down for increasing $P(VAR|HCM)$ and have relatively constant slopes.



(a) Case 3 (b) Case 5 (c) Case 6

Figure S24: deaths, where the $P(VAR|HCM)$ was changed for four different constant values of *# of variants*. Notice how all Cases have negative slopes.

B.7 Discharge Deathrate



(a) Case 2 $\sigma : \{2e{-}4, 2e{-}4, 2e{-}4, 2e{-}4, 2e{-}4\}$

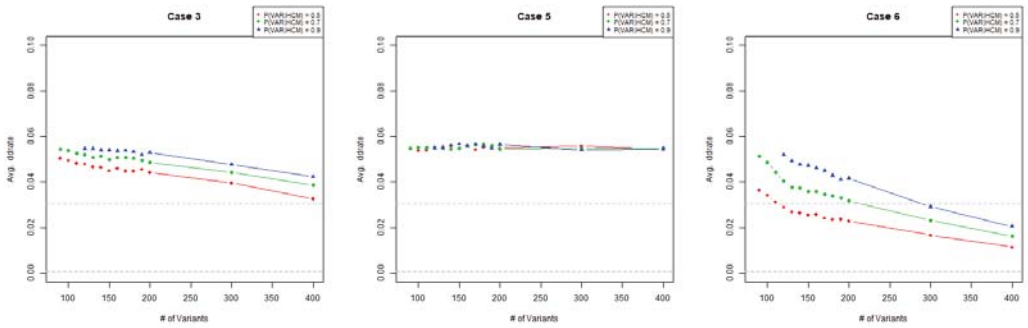
(b) Case 3 $\sigma : \{0.01, 0.02, 0.02, 0.02, 0.02\}$

(c) Case 4 $\sigma : \{9e-3, 9e-3, 9e-3, 0.01, 0.01\}$

(d) Case 5 $\sigma : \{0.02, 0.02, 0.02, 0.02, 0.02\}$

(e) Case 6 $\sigma : \{4e-3, 9e-3, 0.01, 0.01, 0.01\}$

Figure S25: Heatmaps of the average DDrate for each Enlisted case. Standard deviation summary given as: σ: {min, 25th quantile, median, 75th quantile, maximum}.

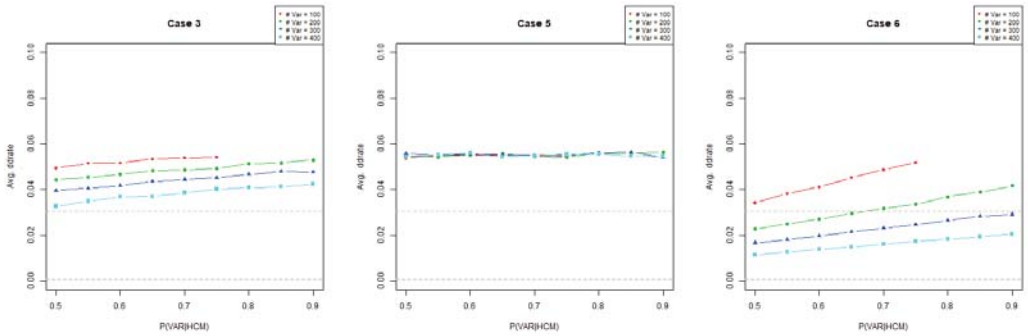


(a) Case 3

(b) Case 5

(c) Case 6

Figure S26: discharge deathrate, where the $\#\ of\ variants$ were changed for three different constant values of $P(VAR|HCM)$. Notice that the slopes of the lines for Case 6 are the most negative, and the slopes of the lines for Case 3 have smaller magnitudes, while Case 5 has nearly flat lines. Increasing $P(VAR|HCM)$ shifts the curves up. Lower Dotted grey line is the average value of DDrate for Case 2, upper dotted grey line is the average value of DDrate for Case 4.



(a) Case 3 (b) Case 5 (c) Case 6

Figure S27: discharge death rate, where the $P(VAR|HCM)$ was changed for four different constant values of $\#\ of\ variants$. Cases 3 and 6 have positive slopes, with Case 6 having a greater slope and more variation in intercepts for different values of $\#\ of\ variants$. Case 5 has flat lines. The lower dotted grey line represents the average value for the DDrate of Case 2, the upper dotted grey line represents the average value for the DDrate of Case 4.

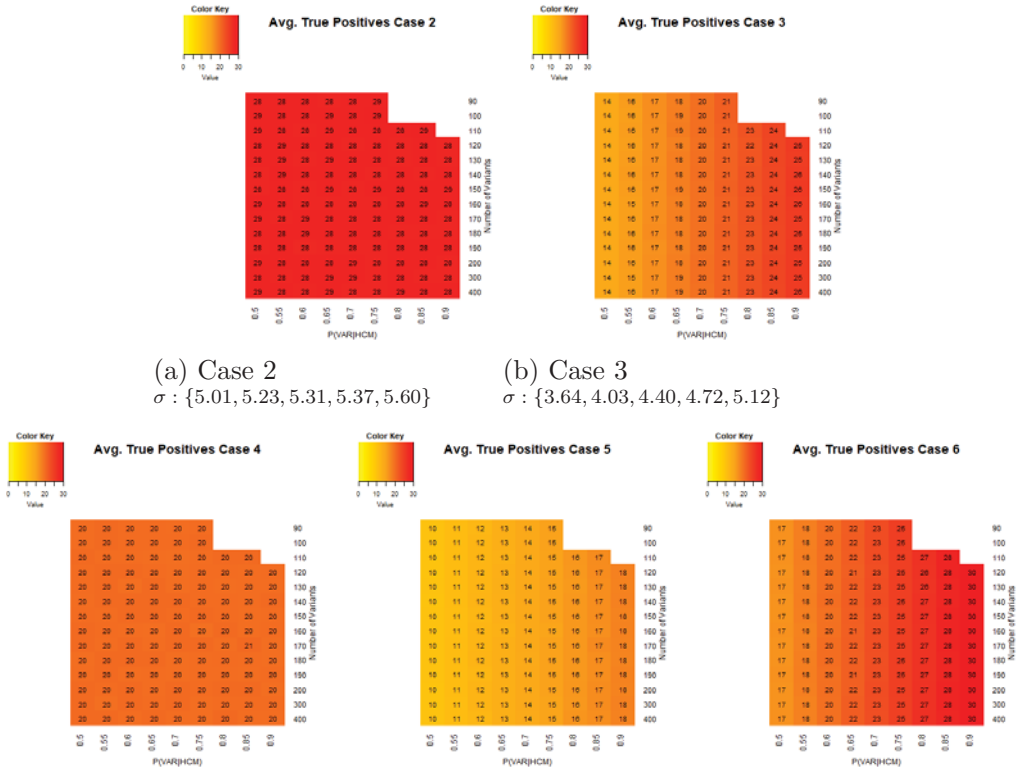
C Appendix: Absolute Number Analysis

In this appendix, we display and explore the trends that occur in the simulations for the absolute numbers in each analysis: the total numbers of True Positives, True Negatives, False Positives and False Negatives in each case.

C.1 True Positives: Number of Individuals Diseased & Discharged

The number of people both discharged and diseased, or true positives (TP), is an indicator of the absolute quantity of how well the screening cases can identify HCM. More true positives indicate that more individuals are being identified as having HCM in a population, and thus the screening test is better at identifying diseased individuals.

Figure S28 displays the average number of True Positives for each combination of $P(VAR|HCM)$ and $\#\ of\ variants$ in the officer simulation over the 1000 iterations. From these heatmaps, it can be seen that Case 2 has a consistently high number of true positives, Case 4 has a consistently lower number of true positives, and cases 3, 5 and 6 vary with the number of true positives with different $P(VAR|HCM)$ and $\#\ of\ variants$ combinations.



(a) Case 2
σ : {5.01, 5.23, 5.31, 5.37, 5.60}

(b) Case 3
σ : {3.64, 4.03, 4.40, 4.72, 5.12}

(c) Case 4
σ : {4.16, 4.41, 4.48, 4.54, 4.69}

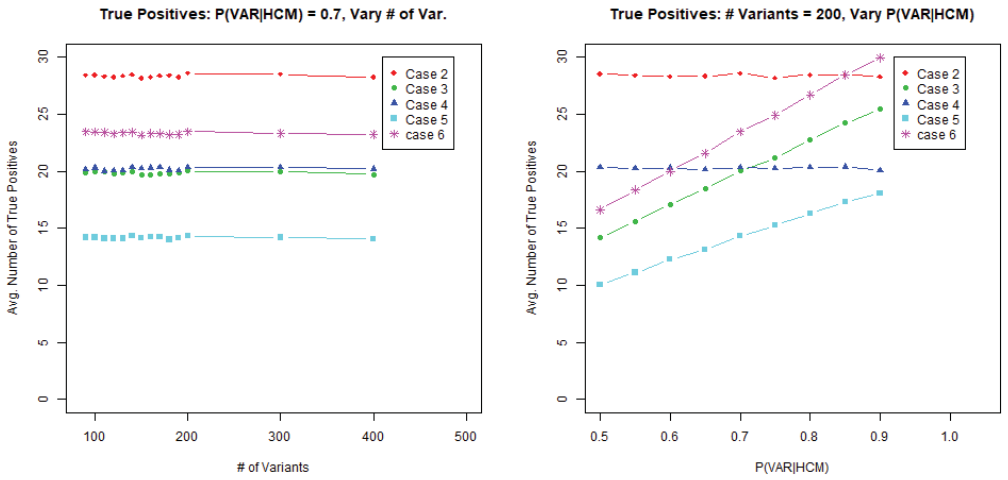
(d) Case 5
σ : {3.07, 3.41, 3.73, 3.96, 4.36}

(e) Case 6
σ : {3.97, 4.36, 4.76, 5.09, 5.59}

Figure S28: Heatmaps of the average number of True Positives for each Officer case. Standard deviation summary given as: σ: {min, 25th quantile, median, 75th quantile, maximum}.

Figure S29 displays graphs of the number of true positives while holding $P(VAR|HCM)$ constant and varying the $\#\ of\ variants$ (Figure S29a), or holding the $\#\ of\ variants$ constant and varying the $P(VAR|HCM)$ (Figure S29b). We can see through this analysis that the number of true positives *does not change* for any case when the number of variants changes, and the true positives *increase* when the $P(VAR|HCM)$ increases for only Cases 3, 5 and 6.

In addition to seeing how the number of true positives changes for different $\#\ of\ variants$ and $P(VAR|HCM)$, we also can gauge from Figures S28 and S29 which cases have an absolute higher number of true positives for any combinations of $\#\ of\ variants$ and $P(VAR|HCM)$. For higher $P(VAR|HCM)$ values, the genetic tests (cases 3,5, and 6) perform better than at lower $P(VAR|HCM)$ values. Case 6 outperforms all other cases at a $P(VAR|HCM)$ of 0.9, however does not perform as well at lower $P(VAR|HCM)$ values. Cases 3 and 5 perform below Case 6, however still increase in performance with increasing $P(VAR|HCM)$.



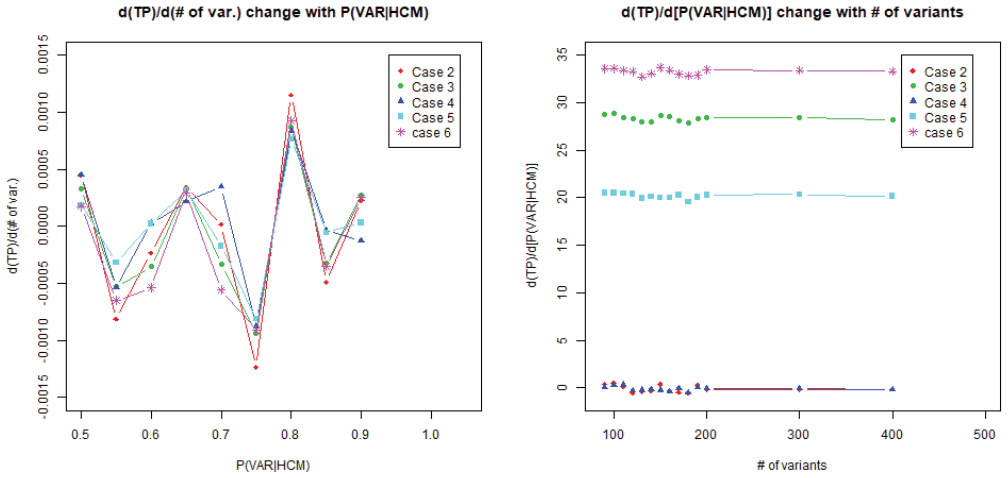
(a) Vary $\#\ of\ Var.$ (b) Vary $P(VAR|HCM)$

Figure S29: Officer Simulation. Average TP does not change significantly for variation of $\#\ of\ variants$. However, cases 3, 5 and 6 increase in TP with increasing $P(VAR|HCM)$.

We can see through Figure S30 that neither $\frac{\partial TP}{\partial \#\ of\ varaints}$ nor $\frac{\partial TP}{\partial P(VAR|HCM)}$ changes with different values of the constants: the variation amoung the values is too small and variable to be considered indicative of a pattern. Additionally, we see in Figure S30b that only the $\frac{\partial TP}{\partial P(VAR|HCM)}$ of cases 3, 5, and 6 are positive for any $\#\ of\ variants$ values, and increases from Case 3 to 5 to 6.

The likely reason for the patterns outlined above are in the fact that with an increasing $P(VAR|HCM)$, more individuals with HCM will have a pathogenic variant, and thus more individuals with HCM will be able to be identified by *genetic* tests, thus increasing the number of true positives for the genetic tests. Non-genetic tests are not affected by this change, however. Case 6 likely has the highest $\frac{\partial TP}{\partial P(VAR|HCM)}$ because it does not have any secondary "check", unlike the echocardiogram follow-up for cases 3 and 5. For cases

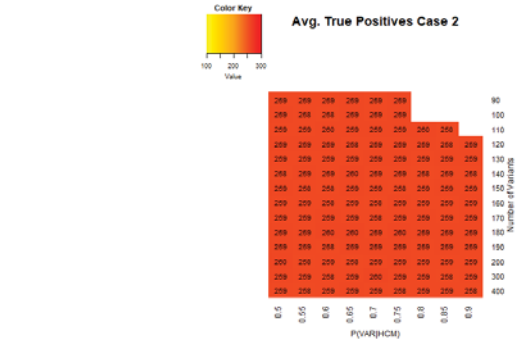
3 and 5, a certian number of individuals who *have* HCM and a variant will be retained due to a false negative echocardiogram. On average, for Case 3, only 85.1% of individuals who have HCM and had a positive genetic test will be discharged, and for Case 5, only 60.7% of individuals who have HCM and a positive genetic test will be discharged (see section 8.3). Because of this "check" that eliminates some true positives, the number of true positives as well as $\frac{\partial TP}{\partial P(VAR|HCM)}$ in cases 3 and 5 will be less than Case 6. Because cases 2 and 4 are non-genetic, they are not affected by the $P(VAR|HCM)$ at all. $\#\ of\ variants$ does not affect even genetic tests because changing the $\#\ of\ variants$ does not change how many people *with HCM* will be identified by a genetic test, but only changes the number of individuals who *do not have* HCM that will be identified by a genetic test.



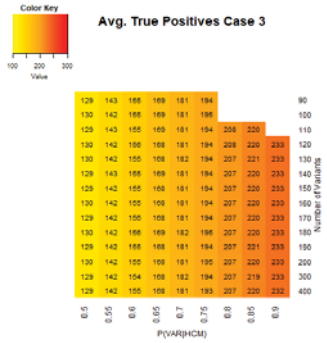
(a) $\frac{\partial TP}{\partial \#\ of\ varaints}$ (b) $\frac{\partial TP}{\partial P(VAR|HCM)}$

Figure S30: Officer Simulation. Values for $\frac{\partial TP}{\partial P(VAR|HCM)}$ are constant with changing $\#\ of\ varaints$, with Case 6 having the highest value, Case 3 the second highest, and Case 5 the third highest. Cases 2 and 4 had slopes of zero. $\frac{\partial TP}{\partial \#\ of\ varaints}$ was around zero for all cases.

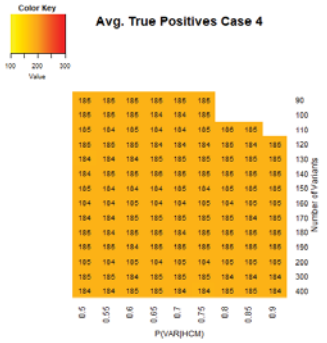
Enlisted simulations returned absolute values of True Positives illustrated in Figure S31. The trends seen in the enlisted cases are the same as the trends seen in the officer cases for $\frac{\partial TP}{\partial \#\ of\ varaints}$ and $\frac{\partial TP}{\partial P(VAR|HCM)}$, with the absolute values being larger due to the larger enlisted population.



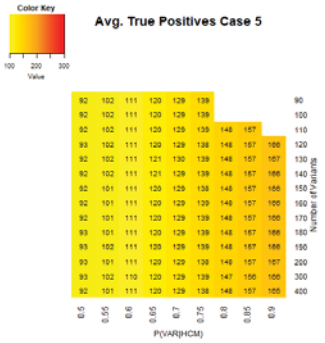
(a) Case 2
σ : $\{15.3, 16.0, 16.2, 16.4, 16.9\}$



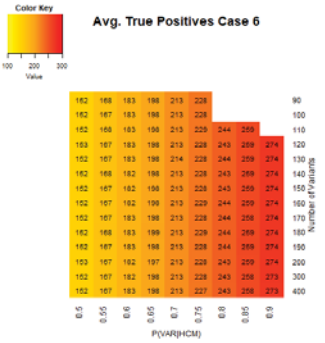
(b) Case 3
σ : $\{11.3, 12.3, 13.3, 14.4, 15.8\}$



(c) Case 4
$\sigma\{12.8, 13.4, 13.7, 13.9, 14.3\}$



(d) Case 5
$\sigma\{9.39, 10.4, 11.3, 12.1, 13.6\}$

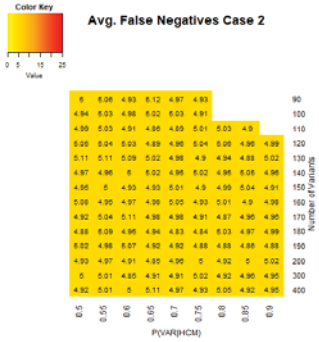


(e) Case 6
σ : $\{12.2, 13.4, 14.6, 15.8, 17.2\}$

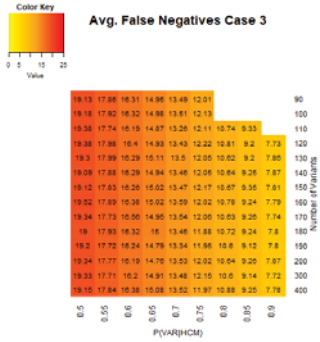
Figure S31: Heatmaps of the average number of True Positives for each enlisted case. Standard deviation summary given as: σ: {min, 25th quantile, median, 75th quantile, maximum}.

C.2 False Negatives: Number of Individuals Diseased and Retained

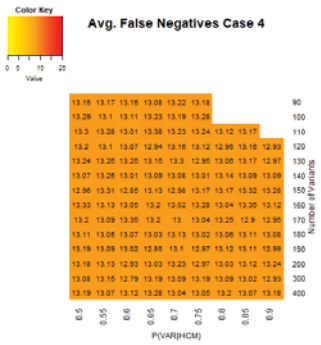
An individual that has HCM that is retained will be at risk of dying from SCD in the military. This diagnostic test must minimize the number of false negatives (FN), or the number of individuals who are diseased and are still retained.



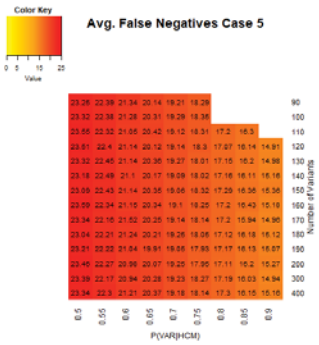
(a) Case 2
σ : {2.05, 2.21, 2.24, 2.27, 2.36}



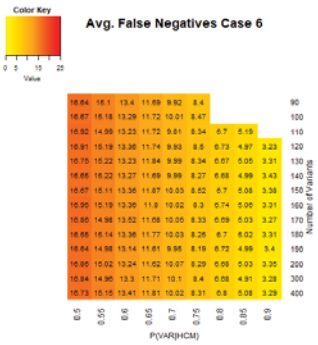
(b) Case 3
σ : {2.70, 3.27, 3.74, 4.13, 4.50}



(c) Case 4
σ {3.41, 3.54, 3.60, 3.65, 3.77}



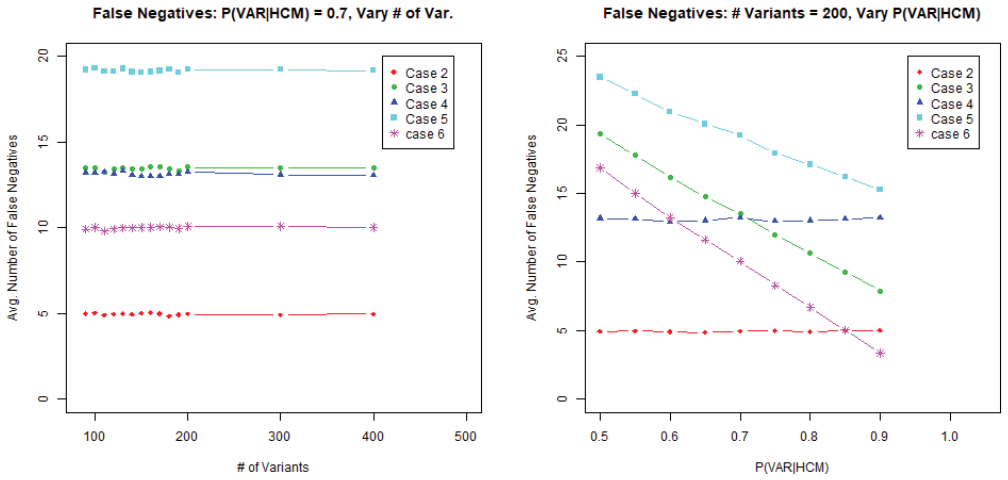
(d) Case 5
σ {3.78, 4.16, 4.40, 4.63, 5.02}



(e) Case 6
σ : {1.76, 2.6, 3.25, 3.71, 4.19}

Figure S32: Heatmaps of the average number of False Positives for each Officer case. Standard deviation summary given as: σ: {min, 25th quantile, median, 75th quantile, maximum}.

Figure S41 displays absolute average values for the false negatives for each $P(VAR|HCM)$ and $\#\ of\ variants$ combination for the 1000 officer simulations. From this figure, it can be seen that Case 2 has a constant low number of false negatives, and cases 3, 5 and 6 lave low numbers of false negatives only for higher $P(VAR|HCM)$ values. Figure S33 displays how the number of false negatives changes with a changing $\#\ of\ variants$ and $P(VAR|HCM)$ holding all other variables constant. From Figure S33a, it can be seen that for the given $P(VAR|HCM)$ of 0.7, Case 5 has the largest number of false negatives, while Case 2 has the lowest number of false negatives, and that the number of false negatives does not appear to change with a changing $\#\ of\ variants$. From Figure S33b, it can be seen that for a $P(VAR|HCM)$ of 0.9, Case 6 has a lower number of FN than Case 2, and that as $P(VAR|HCM)$ increases, Cases 3, 5, and 6 decrease in the number of false negatives.



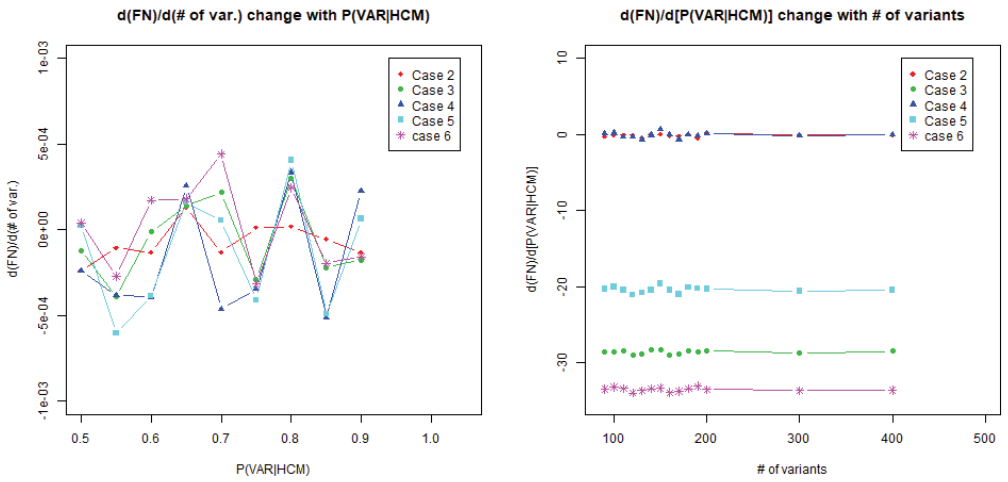
(a) Vary $\# \; of \; Var.$ (b) Vary $P(VAR|HCM)$

Figure S33: The largest amount of FN appears to happen for Case 5 in these figures, and the smallest number of FN happens for both cases 2 and 6 depending on the value of $P(VAR|HCM)$. No change in the FN appears when varying the $\# \; of \; variants$, while the number of FN for cases 3, 5, and 6 decrease for increasing $P(VAR|HCM)$.

Figure S34 displays $\frac{\partial FN}{\partial \# \; of \; varaints}$ and $\frac{\partial FN}{\partial P(VAR|HCM)}$ with varying values of their respective constants. Figure S34a indicates that the number of FN does not change for any value of $\# \; of \; varaints$ regardless of the value of $P(VAR|HCM)$, as the value of $\frac{\partial FN}{\partial \# \; of \; varaints}$ for all cases is approximately zero. Figure S34b indicates that Case 6 has the most negative $\frac{\partial FN}{\partial P(VAR|HCM)}$, followed by Case 3 and Case 5. This means that Case 6 will decrease the number of false negatives in its test more than Case 3 or Case 5 for an increased $P(VAR|HCM)$ no matter the $\# \; of \; varaints$ value.

It is also important to note the pattern we see among the values of $\frac{\partial FN}{\partial P(VAR|HCM)}$ with the values of $\frac{\partial TP}{\partial P(VAR|HCM)}$, which appear to be opposites of each other. For example, for Case 6, a value of $\frac{\partial FN}{\partial P(VAR|HCM)} \backsimeq -34$ can be seen in Figure S33b, and a value of $\frac{\partial TP}{\partial P(VAR|HCM)} \backsimeq 34$ can be seen in Figure S30b. This also happens for cases 3 and 5, and for cases 2 and 4 (which are all zeroes). This makes sense because as a test is able to detect and discharge more individuals who have a disease (increase the TP), the number of individuals who have the disease and are undetected and retained (the number of FN) decreases by the same rate.

Enlisted simulations returned absolute values of False Negatives illustrated in Figure S35. The trends seen in the enlisted cases are the same as the trends seen in the officer cases for $\frac{\partial FN}{\partial \# \; of \; varaints}$ and $\frac{\partial FN}{\partial P(VAR|HCM)}$, with the absolute values being larger due to the larger enlisted population by approximately 9, the ratio of the enlisted population to the officer population.

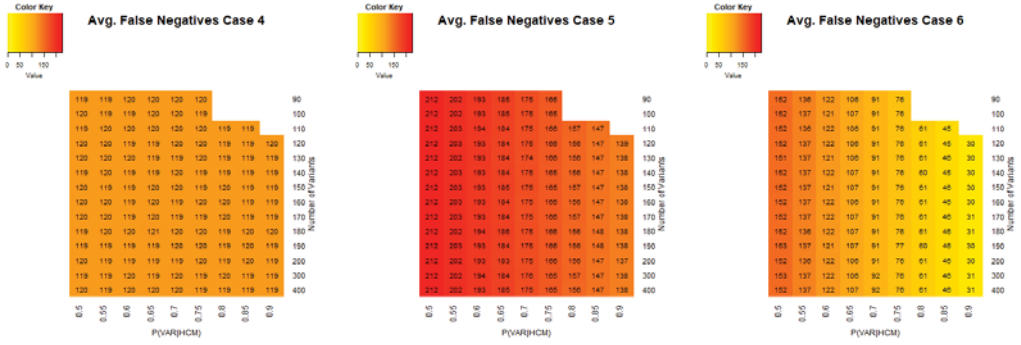


(a) $\frac{\partial FN}{\partial \#\ of\ varaints}$ (b) $\frac{\partial FN}{\partial P(VAR|HCM)}$

Figure S34: $\frac{\partial FN}{\partial \#\ of\ varaints}$ appears to be approximately zero for all cases. $\frac{\partial FN}{\partial P(VAR|HCM)}$ appears to be negative and constant for all values of $\#\ of\ variants$, with increasing magnitude from cases 5, 3 to 6. Note that $\frac{\partial FN}{\partial P(VAR|HCM)}$ appears to be the opposite of $\frac{\partial TP}{\partial P(VAR|HCM)}$.

(a) Case 2
σ : $\{6.40, 6.64, 6.73, 6.86, 7.10\}$

(b) Case 3
σ : $\{8.23, 9.91, 11.1, 12.3, 13.6\}$



(c) Case 4
σ : $\{10.2, 10.8, 11.0, 11.1, 11.6\}$

(d) Case 5
σ : $\{11.3, 12.4, 13.4, 13.9, 15.0\}$

(e) Case 6
σ : $\{5.38, 7.77, 9.62, 11.2, 12.5\}$

Figure S35: Heatmaps of the average number of False Negatives for each enlisted case. Standard deviation summary given as: σ: {min, 25th quantile, median, 75th quantile, maximum}.

C.3 False Positives: Number of Individuals NOT Diseased & Discharged

False Positives (FP) give a measure of how well the screening test is able to discriminate between someone who does not have the disease from someone who has the disease. In this case, discharging someone without disease is a false positive, and has consequences for the military and for the individual. The military will loose a perfectly healthy candidate, and the individual will be prevented from joining the military which has psychological and ethical consequences. In addition, an individual that is flagged as having HCM who does not actually have the disease is brought upon with unnecessary psychological distress from anxiety, additional healthcare requirements, and lifestyle restrictions brought upon from the HCM diagnosis. It is therefore crucial that this test limits the number of people that it erroneously classifies as diseased.

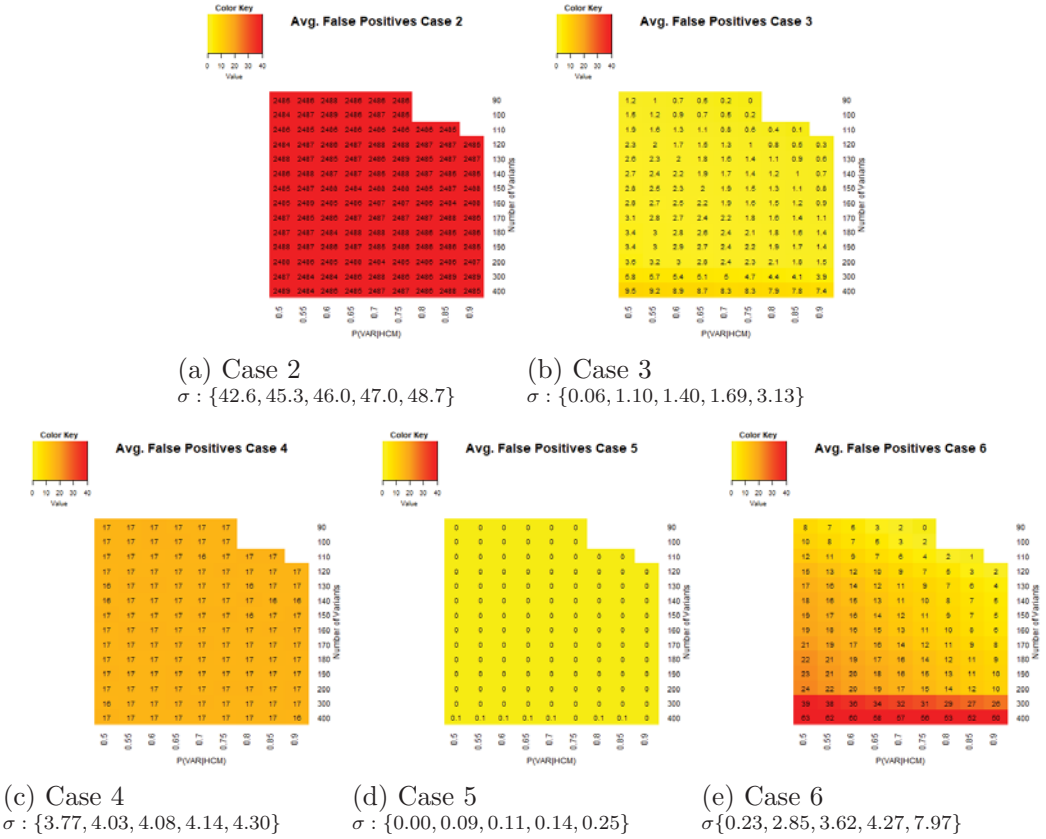
Figure S36 displays the average number of false positives for each $P(VAR|HCM)$ and $\#\ of\ variants$ combination. It can be seen clearly from Figure S36 that Case 2 has a much larger amount of false positives than any of the other cases, and that Case 5 has the lowest number of false positives for every $P(VAR|HCM)$ and $\#\ of\ variants$ combination. Cases 3 and 6 vary in thier false positive values for different $P(VAR|HCM)$ and $\#\ of\ variants$ combinations.

Figures S37 andS38 allow us to see the relative values of FP for each case, and allow us to visualize $\frac{\partial FP}{\partial \#\ of\ varaints}$ and $\frac{\partial FP}{\partial P(VAR|HCM)}$. From Figure S37, the much larger amount of false positives for Case 2 compared with the other cases can be seen. From Figure S38, it can be seen that $\frac{\partial FP}{\partial P(VAR|HCM)}$ is negative for cases 3 and 6, and approximately zero for cases 2, 4 and 5 when the $P(VAR|HCM)$ is held at 0.7. From Figure S37b, it can be seen that $\frac{\partial FP}{\partial \#\ of\ varaints}$ is positive for cases 3 and 6, and zero for cases 2, 4, and 5 when the number of variants is held at 200.

From Figure S39, it can be seen how $\frac{\partial FP}{\partial \#\ of\ varaints}$ and $\frac{\partial FP}{\partial P(VAR|HCM)}$ changes with different constants. Figure S39a shows that $\frac{\partial FP}{\partial \#\ of\ varaints}$ is positive and constant for cases 3 and 6 with Case 6 having the most positive value, and is approximately zero for cases 2, 4 and 5. Figure S39b shows that $\frac{\partial FP}{\partial P(VAR|HCM)}$ is negative constant value for cases 3 and 6 with Case 6 having the most negative value, and is approximatley zero for cases 2, 4 and 5.

The reason for the positive $\frac{\partial FP}{\partial \#\ of\ varaints}$ values for cases 3 and 6 is due to the fact that as more variants are included and recognized as "disease causing," the population of individuals who will be identified by a genetic screening increase. However, for a constant $P(VAR|HCM)$, the number of individuals that actually have HCM remains constant. Because of this fact, the new positives that come from this increase in the number of variants will be false positives. The reason for the negative $\frac{\partial FP}{\partial P(VAR|HCM)}$ for cases 3 and 6 is due to the fact that when the $P(VAR|HCM)$ increases, more individuals who have a variant will have the disease. This will *decrase* the number of people who have the variant and who DO NOT have the disease, thus lowering the false positives.

It is interesting to note that Case 5 has a $\frac{\partial FP}{\partial \#\ of\ varaints}$ and $\frac{\partial FP}{\partial P(VAR|HCM)}$ of close to zero for all $P(VAR|HCM)$ and $\#\ of\ variant$ combinations. This is likely due to the fact that the absolute value of false positves for Case 5 is close to zero, and so the slope for FP will



(a) Case 2
σ : $\{42.6, 45.3, 46.0, 47.0, 48.7\}$

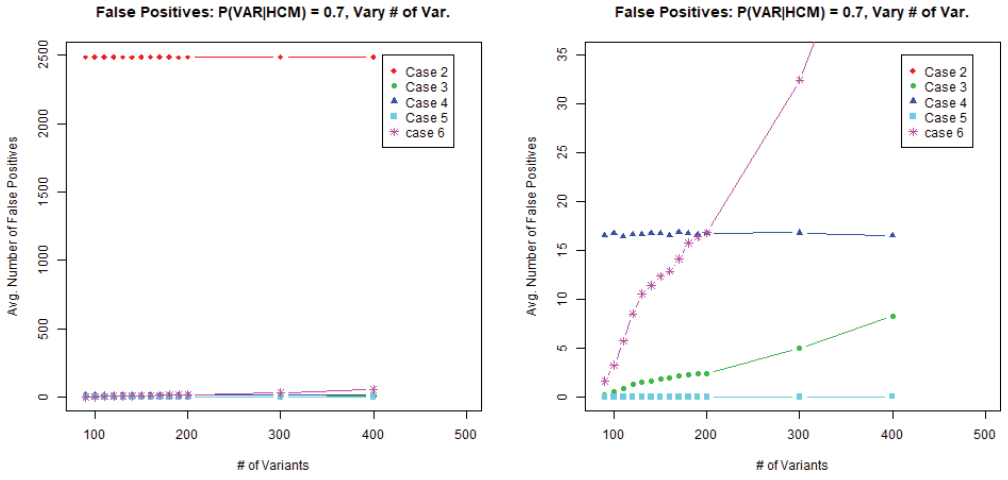
(b) Case 3
σ : $\{0.06, 1.10, 1.40, 1.69, 3.13\}$

(c) Case 4
σ : $\{3.77, 4.03, 4.08, 4.14, 4.30\}$

(d) Case 5
σ : $\{0.00, 0.09, 0.11, 0.14, 0.25\}$

(e) Case 6
$\sigma\{0.23, 2.85, 3.62, 4.27, 7.97\}$

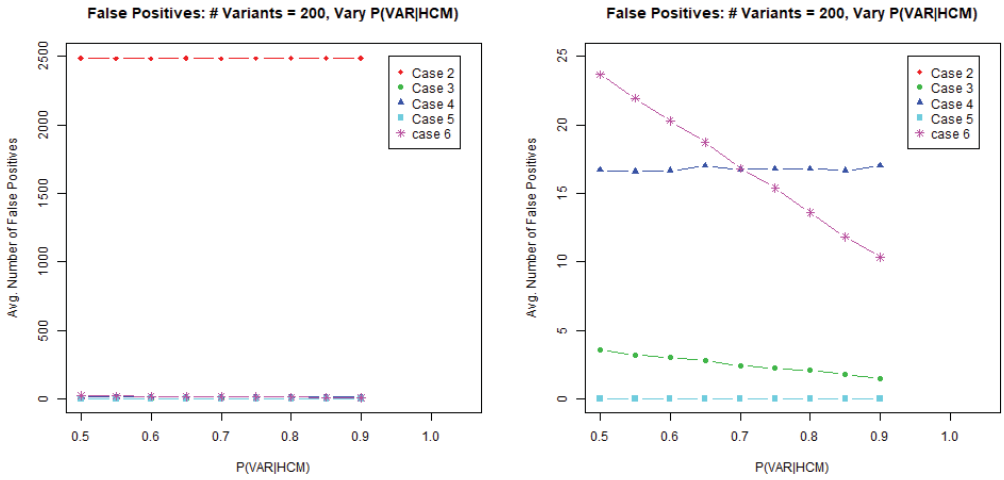
Figure S36: Heatmaps of the average number of False Positives for each Officer case. Standard deviation summary given as: σ: {min, 25th quantile, median, 75th quantile, maximum}.



(a) Zoomed out

(b) Zoomed in

Figure S37: The number of false positives in Case 2 is much larger than the number of false positives in any other case. Additionally, From Figure S37b, it can be seen that the number of FP increases for an increased # *of variants* for cases 3 and 6 only.

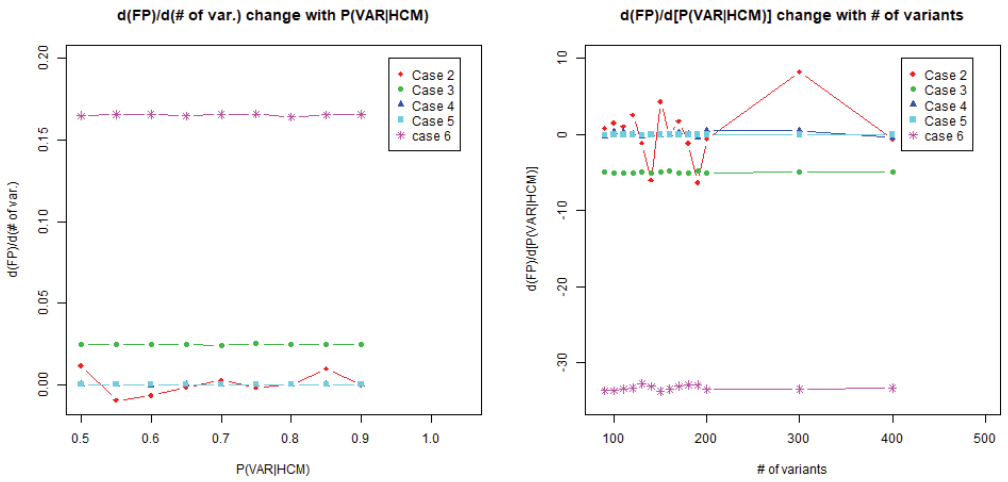


(a) Zoomed out (b) Zoomed in

Figure S38: Again, the number of false positives in Case 2 is much larger than the number of false positives in any other case. Additionally, it can be seen that for cases 3 and 5 only, the number of false positives decreased with an increased $P(VAR|HCM)$.

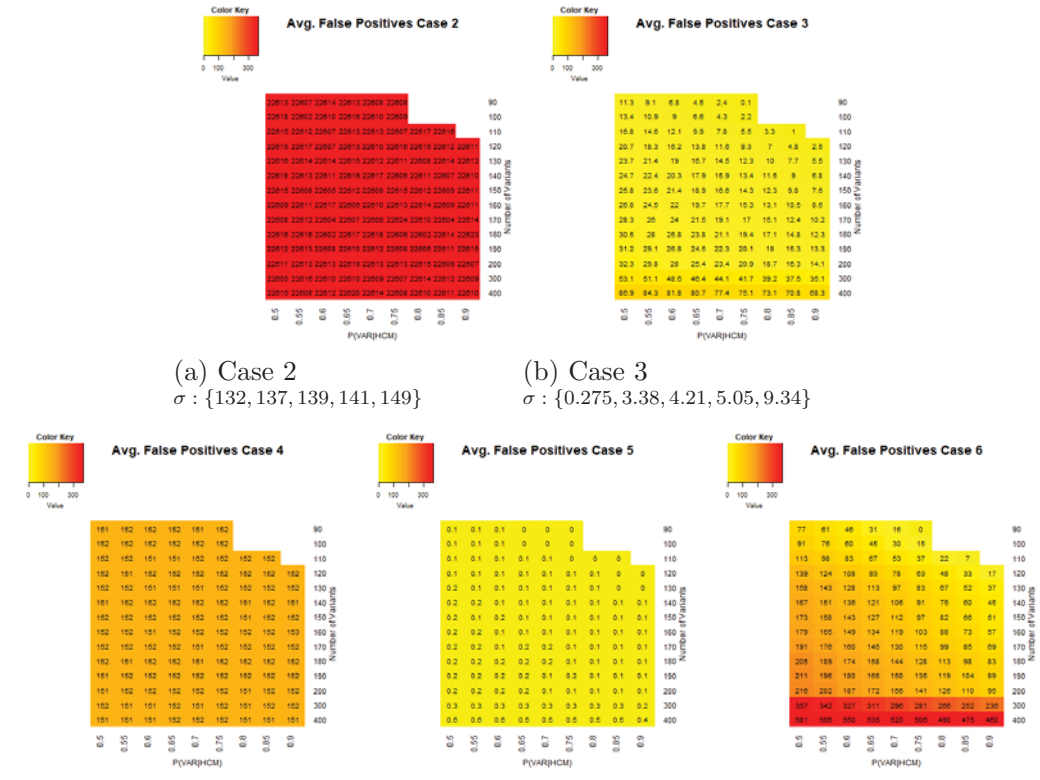
not change much for such low absolute values. Related to this is the fact that Case 3 has much lower absolute values of $\frac{\partial FP}{\partial \#\ of\ varaints}$ and $\frac{\partial FP}{\partial P(VAR|HCM)}$ than Case 6. The reason for this lies in Case 3's echocardiogram "check" on the genetic test, which will also reduce false positives by excluding individuals who do not have HCM yet had a variant and were detected by the genetic test. Cases 2 and 4 are non-genetic, and so would not be expected to change with different values of $P(VAR|HCM)$ or $\#\ of\ variants$.

We display in Figure S40 the average enlisted FP values for the screening test cases. Additionally, we analyzed the trends and $\frac{\partial FP}{\partial \#\ of\ varaints}$ and $\frac{\partial FP}{\partial P(VAR|HCM)}$ as we did for the officer simulations. The trends in the data remained the same, with higher absolute numbers due to the large enlisted population. It is also interesting to note that the values for the enlisted cases are greater than the officer cases by approximately a factor of 9. This is expected because the enlisted population is approximately 9 times as large as the officer population.



(a) Zoomed out (b) Zoomed in

Figure S39: $\frac{\partial FP}{\partial \#\ of\ varaints}$ is seen to be most positive for Case 6, followed by Case 3, and zero for cases 2, 4 and 5. $\frac{\partial FP}{\partial P(VAR|HCM)}$ is seen to be most negative for Case 6, followed by Case 3 and zero for cases 2, 4 and 5. All values appear to be constant for the variation of the constants for the partial derivatives.



(a) Case 2
σ : $\{132, 137, 139, 141, 149\}$

(b) Case 3
σ : $\{0.275, 3.38, 4.21, 5.05, 9.34\}$

(c) Case 4
σ : $\{11.7, 12.1, 12.4, 12.6, 13.1\}$

(d) Case 5
σ : $\{0.032, 0.288, 0.348, 0.424, 0.776\}$

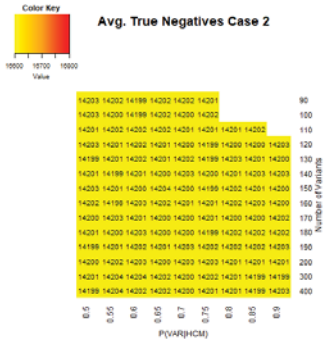
(e) Case 6
σ : $\{0.684, 8.78, 10.9, 13.4, 24.0\}$

Figure S40: Heatmaps of the average number of False Positives for each enlisted case. Standard deviation summary given as: σ: {min, 25th quantile, median, 75th quantile, maximum}.

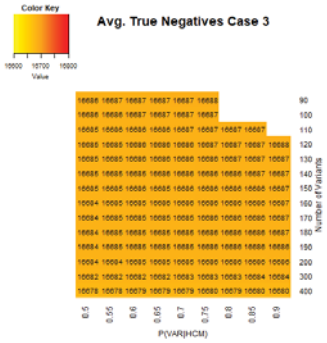
We can make a few conclusions regarding the tests from the data presented. Case 2 produces an extremely large amount of false positives relative to the other cases, and so if a screening test desires to limit false positives, Case 2 would not be a feasible option. The military does need to limit false positives, and so Case 2 would not be a realistic option in the military because of this fact. Case 4 also has a relatively high number of FP. Additionally, cases 3 and 6 performed well by limiting the number of false positives at a high $P(VAR|HCM)$ and low $\#\ of\ variants$, but at lower $P(VAR|HCM)$ and higher $\#\ of\ variant$ combinations, the tests resulted in higher amounts of false positives. This indicates that, in order to use cases 3 and 6, it must be assured that the $P(VAR|HCM)$ and higher $\#\ of\ variant$ values in place in reality are adequate to limit the number of false positives. Case 5 performed well by limiting the number of false positives for every $P(VAR|HCM)$ and $\#\ of\ variant$ combinations.

C.4 True Negatives: Number of individuals NOT Diseased & Retained

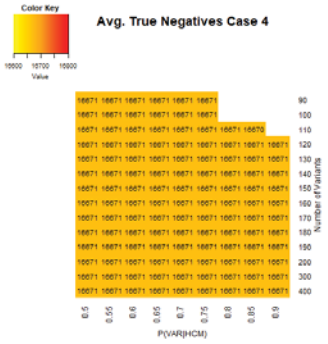
Just as a test must accurately identify people who have a disease without over-classifying disease, a test must also accurately identify individuals who do not have disease. True negatives (TN) convey the number of individuals that are correctly identified as not having disease. Figure S41 displays the absolute values for the number of true negatives for each case and each combination of $P(VAR|HCM)$ and $\#\ of\ variants$ as an average of the 1000 officer simulations. From this data, Case 2 appears to have a much lower number of TN than the other cases, and Case 6 appears to have variability in TN for different $P(VAR|HCM)$.



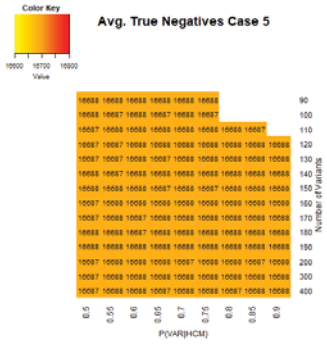
(a) Case 2
σ : {43.08, 45.59, 46.31, 47.19, 48.94}



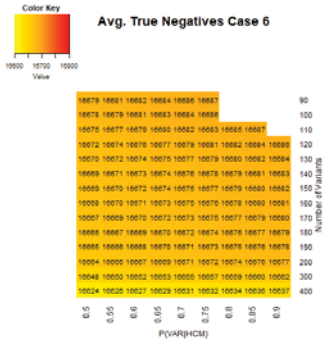
(b) Case 3
σ : {5.54, 5.81, 5.88, 6.02, 6.63}



(c) Case 4
σ : {6.64, 6.92, 7.05, 7.14, 7.41}



(d) Case 5
σ : {5.44, 5.66, 5.73, 5.80, 6.01}

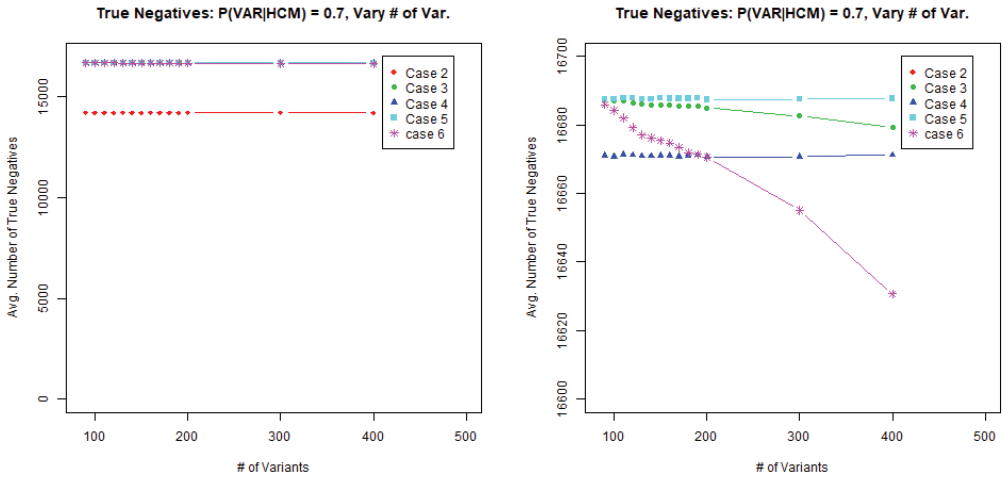


(e) Case 6
σ : {5.54, 6.38, 6.74, 7.15, 9.95}

Figure S41: Heatmaps of the average number of True Negatives for each Officer case. Standard deviation summary given as: σ: {min, 25th quantile, median, 75th quantile, maximum}.

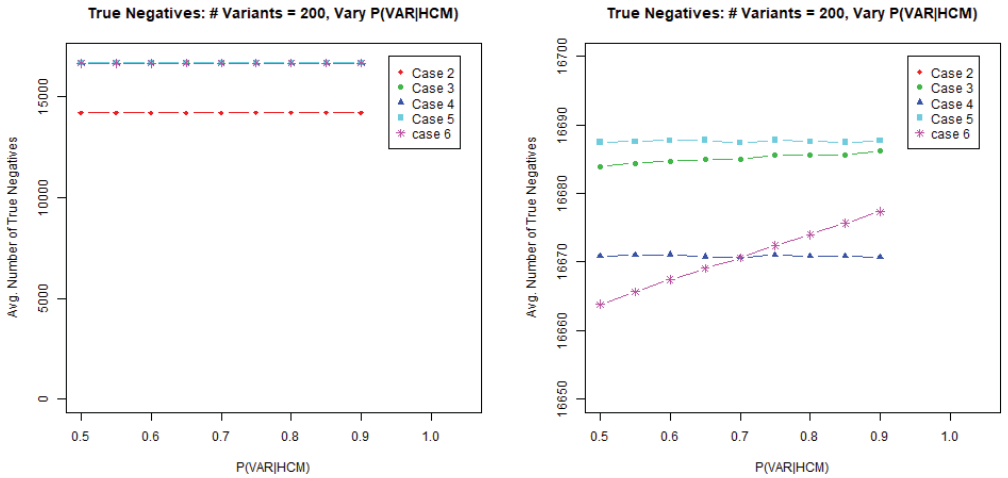
From Figures S42a and S43a, it can be seen that the number of TN is much less for Case 2 than the other cases. From Figure S42b, a negative slope, $\frac{\partial TN}{\partial \#\ of\ varaints}$, can be seen for cases 3 and 6. This indicates that the number of TN decreases for an increased number of variants. From Figure S43b, a positive slope, $\frac{\partial TN}{\partial P(VAR|HCM)}$, is found for cases 3 and 6, indicating that the number of TN increases with an increased $P(VAR|HCM)$.

Figure S44 displays the values of $\frac{\partial TN}{\partial \#\ of\ varaints}$ and $\frac{\partial TN}{\partial P(VAR|HCM)}$ for all of their respective constants. From Figure S44a, $\frac{\partial TN}{\partial \#\ of\ varaints}$ appears to be its most negative for Case 6,



(a) Zoomed out (b) Zoomed in

Figure S42: The number of true negatives in Case 2 is much smaller than the number of true negatives in any other case. Additionally, From Figure S42b, it can be seen that the number of TN decreases for an increased $\#\ of\ variants$ for cases 3 and 6 only.



(a) Zoomed out (b) Zoomed in

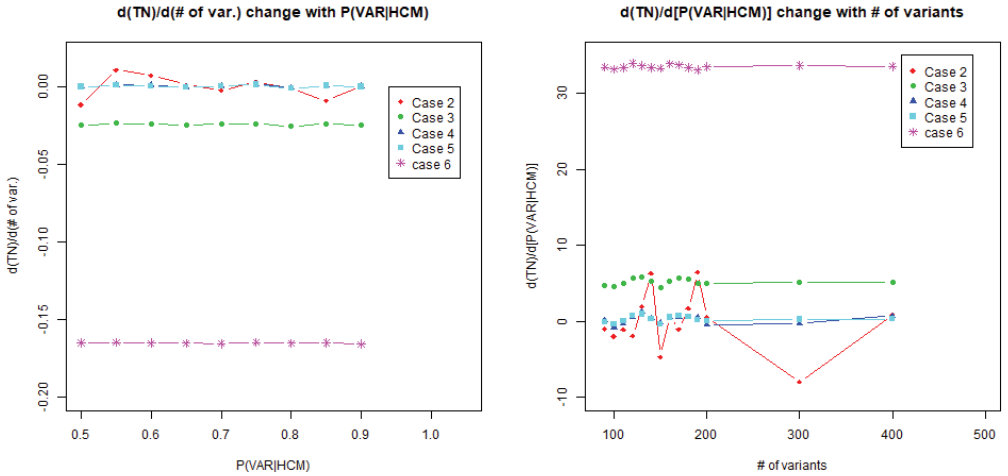
Figure S43: Again, the number of true negatives in Case 2 is much smaller than the number of true negatives in any other case. Additionally, it can be seen that for cases 3 and 5 only, the number of true negatives increased with an increased $P(VAR|HCM)$.

followed by Case 3, and zero for cases 2, 4 and 5. From Figure S44b, $\frac{\partial TN}{\partial P(VAR|HCM)}$ appears to be largest for Case 6, followed by Case 3, and zero for cases 2, 4 and 5 (Case 5 may possibly have a very slightly positive value).

It is important to note the pattern we see between the true negative results and the true positive results. The true negative results appear to have the opposite trends as the true positive results: for an increased $P(VAR|HCM)$, the number of true negatives rise while

the number of false positives fall, and for an increased $\#\ of\ variants$, the number of true negatives fall while the number of true positives rise. Even more interesting to note are the values of $\frac{\partial TN}{\partial \#\ of\ varaints}$ and $\frac{\partial TN}{\partial P(VAR|HCM)}$ compared with the values of $\frac{\partial FP}{\partial \#\ of\ varaints}$ and $\frac{\partial FP}{P(VAR|HCM)}$. For the same case, the numbers appear to be direct opposites of each other. For example, for Case 6, a value of $\frac{\partial FP}{\partial \#\ of\ varaints} \backsimeq 0.16$ for all values of $P(VAR|HCM)$, and a value of $\frac{\partial TN}{\partial \#\ of\ varaints} \backsimeq -0.16$ for all values of $P(VAR|HCM)$ are found. Additionally, a value of $\frac{\partial FP}{P(VAR|HCM)} \backsimeq -35$ for all values of $\#\ of\ variants$, and a value of $\frac{\partial TN}{\partial P(VAR|HCM)} \backsimeq 35$ for all values of $\#\ of\ variants$ are found for Case 6. The same is true for the other cases: it appears that the values for the partial derivatives of the false positives are *opposites* of the partial derivatives for the true negatives. This observation makes sense because, as a test is able to distinguish better which individuals do NOT have disease, or in this case do not have HCM, the number of falsely classified individuals as diseased will decrease, and the number of correctly classified individuals as NOT diseased will increase, thus decreasing the number of false positives and increasing the number of true negatives at the same rate.

Thus, when discussing the trends in data for true negatives, the trends may also be explained by the false positives. For the genetic cases, the tests will become better at not misclassifying individuals as diseased for lower values of $\#\ of\ variants$ larger values of $P(VAR|HCM)$. Case 6, again, appears to have a greater change in TN values than the other genetic tests (cases 3 and 5) because there is no ability to "check" Case 6, unlike cases 3 and 5, and so it will be more affected by the changing parameters of $\#\ of\ variants$ and $P(VAR|HCM)$.

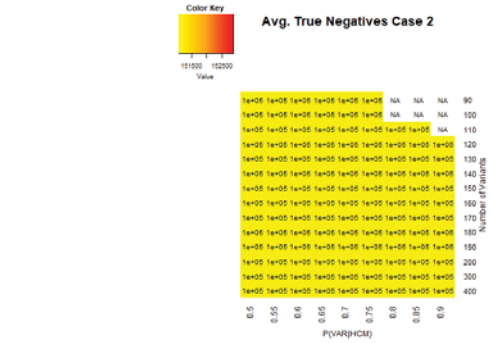


(a) $\frac{\partial TN}{\partial \#\ of\ varaints}$ (b) $\frac{\partial TN}{\partial P(VAR|HCM)}$

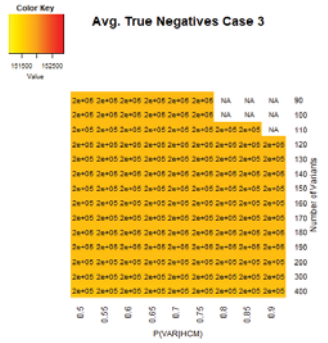
Figure S44: $\frac{\partial TN}{\partial \#\ of\ varaints}$ is seen to be most negative for Case 6, followed by Case 3, and zero for cases 2, 4 and 5. $\frac{\partial TN}{\partial P(VAR|HCM)}$ is seen to be most positive for Case 6, followed by Case 3 and zero for cases 2, 4 and 5. All values appear to be constant for the variation of the constants for the partial derivatives.

In Figure S45, the average values over the 1000 enlisted simulations for each $\#\ of\ variants$

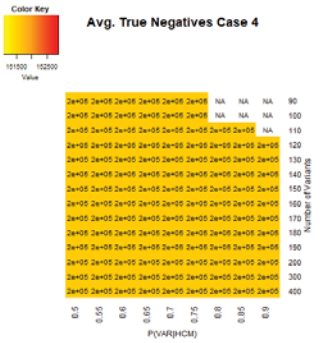
and $P(VAR|HCM)$ combination are shown. These trends are the same except the absolute value of the numbers is increased by approximately 9, the approximate ratio of the enlisted population to the officer population.



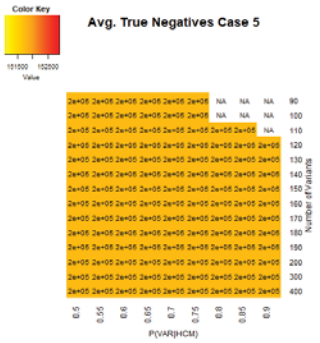
(a) Case 2
σ : $\{132, 138, 140, 141, 149\}$



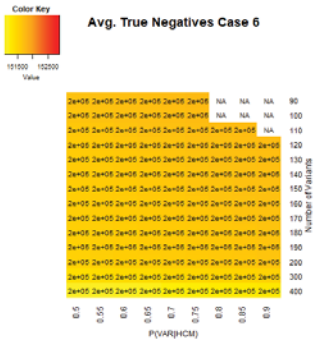
(b) Case 3
σ : $\{16.8, 17.8, 18.1, 18.5, 20.0\}$



(c) Case 4
σ : $\{20.2, 21.2, 21.5, 21.8, 22.5\}$



(d) Case 5
σ : $\{16.6, 17.3, 17.5, 17.8, 18.5\}$



(e) Case 6
σ : $\{17.3, 19.8, 21.0, 22.2, 29.9\}$

Figure S45: Heatmaps of the average number of True Negatives for each enlisted case. Standard deviation summary given as: σ: {min, 25th quantile, median, 75th quantile, maximum}.

D Appendix: Additional Information

In this Appendix, we include a Table displaying the raking of all possible logistic regression models (Table S1), a Table displaying the ranking of all 400 variants used in the ranked variant list (Table S2), and the approval documents, actual survey form distributed, and survey email distributed to individuals at the United States Naval Academy.

Supplementary Table S1: A Ranking of All Possible Models

This table lists all 64 logistic regression models as ranked by AIC for how well they fit the ClinVar data for HCM in MYH7 and MYBPC3 according to AIC. Boxes filled in black indicate the presence of a parameter in the model.

Model #	Allele Frequency	Gerp	CADD	Splice Indicator	Vertebrate PhyloP	AA Change?	Conservative Change?	MYH7 Rank	MYBPC3 Rank	MYBPC3 + MYH7 Rank	Total Rank Number	Rank
46	■		■	■		■		5	4	1	10	1
122	■			■	■	■	■	11	2	3	16	2
121				■	■	■	■	7	6	8	21	3
110	■		■	■		■	■	10	7	2	19	4
44	■	■		■		■		4	9	4	17	5
45			■	■		■		2	10	6	18	6
58	■			■	■	■		18	1	7	26	7
57				■	■	■		12	5	10	27	8
109			■	■		■	■	6	14	9	29	9
108	■	■		■		■	■	9	13	5	27	10
43		■		■		■		1	17	13	31	11
78	■		■	■			■	8	11	11	30	12
107		■		■		■	■	3	19	12	34	13
14	■		■	■				17	8	15	40	14
29			■	■	■			25	3	14	42	15
77			■	■			■	22	12	16	50	16
13			■	■				27	15	17	59	17
106	■			■		■	■	36	18	18	72	18
38	■		■			■		13	29	20	62	19
42	■			■		■		35	16	19	70	20

70	■		■				■	16	30	23	69	21
105				■		■	■	34	22	21	77	22
41				■		■		33	23	25	81	23
90	■			■	■		■	41	20	24	85	24
102	■		■			■	■	20	33	22	75	25
89				■	■		■	43	21	26	90	26
36	■	■				■		19	34	33	86	27
37			■			■		15	47	27	89	28
35		■				■		14	43	41	98	29
50	■				■	■		30	28	32	90	30
100	■	■				■	■	24	39	34	97	31
101			■			■	■	23	49	29	101	32
76	■	■		■			■	46	24	35	105	33
114	■				■	■	■	31	31	30	92	34
99		■				■	■	21	46	40	107	35
75		■		■			■	47	25	38	110	36
69			■				■	26	45	28	99	37
49					■	■		28	35	37	100	38
5			■					32	41	31	104	39
113					■	■	■	29	37	36	102	40
82	■				■		■	42	32	39	113	41
26	■			■	■			50	26	44	120	42
81					■		■	44	36	42	122	43
25				■	■			53	27	46	126	44
68	■	■					■	45	40	43	128	45
67		■					■	48	44	45	137	46
98	■					■	■	39	56	49	144	47

34	■					■		40	55	50	145	48
18	■				■			49	50	47	146	49
97						■	■	37	60	55	152	50
74	■			■			■	52	48	48	148	51
12	■	■		■				58	38	52	148	52
33						■		38	61	56	155	53
17					■			54	51	51	156	54
11		■		■				60	42	57	159	55
73				■			■	56	52	53	161	56
4	■	■						57	53	54	164	57
66	■						■	51	58	59	168	58
3		■						59	54	58	171	59
65							■	55	62	60	177	60
10	■			■				62	57	61	180	61
2	■							61	63	62	186	62
9				■				64	59	63	186	63
1								63	64	64	191	64

Supplementary Table S2: Top 400 Variants on Ranked Variant List

This table lists the top 400 variants according to their position on the ranked variant list for MYH7 and MYBPC3. These variants were used in the cost/benefit simulation. We include these variants as a reference and as a tool for future exploration in genomic variation, with the possibility that variants on this list may be validated as pathogenic by future genomic discoveries. The First 90 variants, all ranked 1, are pathogenic according to ClinVar. The next 310 variants, not found in ClinVar, are ranked according to their model score.

Rank	Chrom.	Pos.	Ref.	Alt.	Model #46 Score
1	11	47353795	C	T	1
1	11	47360071	C	T	1
1	11	47369975	C	T	1
1	14	23886078	T	G	1
1	14	23889431	C	A	1
1	11	47353626	G	A	1
1	11	47356671	G	A	1
1	11	47364129	C	G	1
1	11	47353740	G	A	1
1	11	47355117	G	A	1
1	11	47368981	T	A	1
1	14	23884229	C	T	0.999
1	11	47367757	C	A	0.999
1	14	23884353	C	T	0.999
1	14	23883305	C	T	0.999
1	14	23886382	C	T	0.999
1	11	47359010	C	T	0.999
1	14	23897840	C	T	0.999
1	14	23894048	C	T	0.999
1	14	23888796	C	G	0.999
1	11	47370000	G	T	0.999
1	14	23893328	G	A	0.998
1	14	23888475	C	T	0.998
1	11	47355304	C	T	0.998
1	14	23892818	C	T	0.998
1	14	23898246	C	T	0.998
1	14	23894567	G	A	0.998
1	14	23892761	C	T	0.998
1	11	47353433	C	T	0.998
1	14	23886827	G	A	0.997
1	11	47354526	T	G	0.997
1	11	47355107	C	T	0.997
1	11	47364667	C	T	0.997

1	14	23895180	G	A	0.997
1	14	23894969	C	T	0.997
1	14	23893234	T	A	0.996
1	11	47368581	C	G	0.995
1	14	23901922	C	T	0.995
1	14	23888731	C	T	0.994
1	14	23889439	C	T	0.994
1	11	47355106	A	C	0.994
1	11	47369407	C	T	0.993
1	11	47364269	C	T	0.993
1	11	47367768	C	G	0.993
1	11	47359005	A	G	0.993
1	14	23900999	G	A	0.992
1	14	23893321	T	C	0.992
1	11	47354743	A	C	0.992
1	11	47374196	C	G	0.991
1	14	23896932	C	G	0.991
1	11	47360114	G	T	0.99
1	14	23896042	C	T	0.99
1	11	47364698	T	C	0.989
1	14	23895023	G	A	0.989
1	11	47367923	T	C	0.988
1	11	47360200	C	T	0.987
1	14	23900635	A	G	0.987
1	14	23892881	G	T	0.986
1	11	47373058	T	C	0.986
1	11	47364270	G	C	0.986
1	11	47364632	C	T	0.985
1	11	47364580	A	G	0.984
1	14	23897049	C	T	0.984
1	14	23900859	C	T	0.982
1	14	23902297	A	G	0.98
1	14	23892845	G	C	0.979
1	11	47354203	G	C	0.977
1	14	23902913	C	G	0.976
1	11	47367764	T	C	0.973
1	14	23896982	C	T	0.971
1	14	23896866	C	T	0.97
1	14	23886150	T	C	0.969
1	14	23884256	G	C	0.967
1	11	47354848	T	C	0.964
1	14	23893316	G	C	0.961
1	14	23894013	G	C	0.937

1	14	23883216	C	T	0.936
1	11	47354740	C	T	0.929
1	11	47354740	C	G	0.913
1	11	47363612	G	A	0.906
1	14	23894525	C	T	0.897
1	11	47355103	C	T	0.889
1	11	47364125	T	A	0.879
1	14	23900992	T	C	0.85
1	11	47365119	G	C	0.842
1	14	23885003	G	T	0.719
1	11	47371575	C	G	0.602
1	11	47367930	C	T	0.541
1	11	47364832	C	T	0.001
1	11	47364709	C	T	0.001
91	14	23890256	T	A	1
92	11	47353625	C	T	1
93	14	23895986	C	T	1
94	14	23883101	T	C	1
95	14	23885041	C	T	1
96	11	47363542	C	T	1
97	14	23900886	C	T	1
98	14	23886513	C	T	1
99	14	23883310	G	A	1
100	14	23883237	G	T	1
101	14	23894232	C	A	1
102	11	47354209	C	A	1
103	14	23889176	C	A	1
104	14	23889224	C	A	1
105	14	23898166	C	T	1
106	11	47354524	C	T	1
107	14	23885290	C	A	1
108	14	23886827	G	T	1
109	14	23892767	G	A	1
110	14	23884990	C	A	1
111	11	47371326	T	A	1
112	11	47353809	G	A	1
113	14	23887614	G	C	1
114	14	23885041	C	A	1
115	14	23886133	G	A	1
116	14	23888427	G	A	1
117	14	23887614	G	A	1
118	14	23893357	T	A	1
119	11	47353809	G	T	1

120	14	23893277	C	A	1
121	14	23888451	G	A	1
122	14	23894010	C	A	1
123	14	23886491	G	A	1
124	14	23896796	G	A	1
125	14	23885482	G	A	1
126	11	47372053	C	G	1
127	11	47358942	C	T	1
128	14	23897831	G	A	1
129	14	23902303	C	T	0.999
130	14	23888773	C	CA	0.999
131	14	23896918	G	T	0.999
132	14	23896511	C	A	0.999
133	14	23902302	C	T	0.999
134	14	23891486	G	A	0.999
135	14	23884442	TC	T	0.999
136	14	23887429	C	T	0.999
137	14	23888410	C	CT	0.999
138	14	23888450	C	T	0.999
139	14	23891485	C	G	0.999
140	14	23893340	C	CAT	0.999
141	14	23894102	A	AT	0.999
142	14	23894186	AC	A	0.999
143	14	23894201	C	T	0.999
144	14	23894542	TG	T	0.999
145	14	23896822	CAG	C	0.999
146	14	23900678	G	A	0.999
147	14	23885265	CG	C	0.999
148	14	23890185	C	A	0.999
149	14	23893342	GCC	G	0.999
150	14	23882985	G	A	0.999
151	14	23884294	C	CAT	0.999
152	14	23884291	ATT	A	0.999
153	14	23885480	CTGGGCCCGGAGGATCT	C	0.999
154	11	47363692	AC	A	0.999
155	14	23885484	GC	G	0.999
156	11	47354131	G	A	0.999
157	14	23887577	C	CCGGGCCGACTG	0.999
158	11	47356663	CCG	C	0.999
159	14	23889355	TC	T	0.999
160	11	47362772	T	TCG	0.999
161	11	47354884	T	TCAACAAC	0.999
162	14	23883068	C	T	0.999

163	14	23888796	C	T	0.999
164	11	47354119	TG	T	0.999
165	14	23883054	C	T	0.999
166	14	23894536	C	T	0.999
167	14	23895227	C	T	0.999
168	14	23886764	C	T	0.999
169	14	23888716	G	A	0.999
170	11	47354175	C	A	0.999
171	11	47354176	G	A	0.999
172	11	47353660	CT	C	0.999
173	11	47355200	C	T	0.999
174	14	23889187	TC	T	0.999
175	14	23883021	C	T	0.999
176	14	23883069	G	A	0.999
177	14	23888492	C	T	0.999
178	14	23894494	C	T	0.999
179	14	23883283	C	T	0.999
180	14	23886807	G	A	0.999
181	14	23887443	C	T	0.999
182	14	23890220	C	T	0.999
183	14	23891405	C	A	0.999
184	14	23892815	C	T	0.999
185	14	23894177	C	A	0.999
186	14	23895228	G	A	0.999
187	14	23896832	A	AG	0.999
188	14	23898175	C	T	0.999
189	14	23901892	TG	T	0.999
190	14	23901905	C	T	0.999
191	14	23886132	C	T	0.999
192	14	23902892	C	T	0.999
193	11	47364285	C	G	0.999
194	11	47367776	C	A	0.999
195	14	23884860	C	G	0.999
196	14	23887567	C	T	0.999
197	14	23887579	G	A	0.999
198	11	47353644	C	T	0.999
199	14	23889167	C	T	0.999
200	11	47359002	C	T	0.999
201	11	47364429	C	T	0.999
202	11	47370000	GCAGT	G	0.999
203	11	47365121	CG	C	0.999
204	11	47365122	G	GGA	0.999
205	14	23884233	C	T	0.999

206	11	47365110	C	T	0.999
207	11	47371406	C	A	0.999
208	11	47355138	C	T	0.999
209	11	47355129	TG	T	0.999
210	11	47360120	C	CA	0.999
211	14	23883032	C	T	0.999
212	14	23888804	CT	C	0.999
213	11	47356670	C	T	0.999
214	11	47358988	G	GA	0.999
215	11	47358987	C	A	0.999
216	14	23882996	C	T	0.999
217	14	23895172	C	T	0.999
218	14	23884376	C	T	0.999
219	14	23885403	C	T	0.999
220	14	23891465	C	T	0.999
221	14	23900798	C	T	0.999
222	14	23886457	C	T	0.999
223	14	23891426	C	T	0.999
224	11	47353722	C	T	0.999
225	11	47359094	C	G	0.999
226	14	23883009	C	A	0.999
227	11	47360200	C	A	0.999
228	11	47359001	G	A	0.999
229	11	47355201	G	A	0.999
230	14	23891500	C	A	0.999
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233	11	47355156	G	A	0.999
234	11	47360208	C	T	0.999
235	14	23889202	C	T	0.999
236	11	47358987	C	T	0.999
237	14	23889373	C	T	0.999
238	14	23889280	C	T	0.999
239	11	47363567	G	A	0.999
240	11	47359094	C	T	0.999
241	11	47360104	C	T	0.999
242	14	23884899	C	T	0.999
243	14	23883059	T	A	0.998
244	14	23884377	G	A	0.998
245	14	23884422	G	A	0.998
246	14	23884449	C	T	0.998
247	14	23885344	G	A	0.998
248	14	23885392	G	A	0.998

249	11	47353764	C	T	0.998
250	14	23884909	C	T	0.998
251	11	47367805	A	ATGCCG	0.998
252	11	47359029	C	G	0.998
253	14	23885488	G	A	0.998
254	11	47367866	C	T	0.998
255	11	47367890	C	T	0.998
256	14	23883033	G	A	0.998
257	14	23885343	C	T	0.998
258	14	23888502	C	T	0.998
259	11	47359053	G	GA	0.998
260	11	47359074	C	T	0.998
261	14	23886115	C	T	0.998
262	14	23902893	G	A	0.998
263	11	47367809	C	T	0.998
264	14	23883284	G	A	0.998
265	14	23893115	C	T	0.998
266	11	47355528	C	T	0.998
267	11	47353754	C	T	0.998
268	14	23889256	C	T	0.998
269	14	23889251	C	T	0.998
270	11	47360874	C	T	0.998
271	11	47354130	C	T	0.998
272	11	47353638	G	A	0.998
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274	11	47361267	G	A	0.998
275	14	23884421	C	T	0.998
276	14	23885487	C	T	0.998
277	14	23884310	C	T	0.998
278	14	23895028	C	A	0.998
279	11	47362755	C	T	0.998
280	14	23886190	C	T	0.998
281	14	23887513	G	A	0.998
282	14	23884999	C	T	0.998
283	14	23884311	G	A	0.998
284	14	23902905	C	T	0.998
285	11	47355189	G	A	0.998
286	14	23895201	G	A	0.998
287	14	23886717	C	T	0.998
288	11	47365047	C	G	0.998
289	11	47359280	A	AC	0.998
290	14	23884929	C	T	0.998
291	11	47354115	A	T	0.998

292	14	23883098	T	C	0.998
293	14	23884344	C	T	0.998
294	14	23885305	C	T	0.998
295	14	23887429	C	G	0.998
296	14	23890219	T	C	0.998
297	14	23893217	G	T	0.998
298	14	23899017	G	A	0.998
299	14	23884903	AC	A	0.998
300	11	47363693	C	T	0.998
301	11	47367826	C	A	0.998
302	11	47354136	G	A	0.998
303	14	23887567	C	G	0.998
304	11	47367838	G	A	0.998
305	14	23889158	C	G	0.998
306	11	47372982	CTG	C	0.998
307	14	23888493	G	A	0.998
308	14	23889334	C	T	0.998
309	14	23884966	G	A	0.998
310	14	23889359	G	A	0.998
311	11	47370035	G	A	0.998
312	14	23884304	C	T	0.998
313	14	23887512	C	T	0.998
314	14	23894049	G	A	0.998
315	14	23895255	G	A	0.998
316	14	23884905	C	T	0.998
317	14	23889323	C	T	0.998
318	14	23884965	C	T	0.998
319	11	47354443	G	A	0.998
320	14	23887557	C	T	0.998
321	14	23886518	C	T	0.998
322	11	47364296	C	G	0.998
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324	14	23883071	A	G	0.998
325	14	23886133	G	C	0.998
326	11	47359001	G	C	0.998
327	11	47359041	G	A	0.998
328	14	23894051	C	T	0.998
329	14	23887546	C	T	0.998
330	14	23883224	C	T	0.998
331	14	23895200	C	A	0.998
332	14	23883233	G	A	0.998
333	11	47355118	CA	C	0.998
334	11	47355233	C	T	0.998

335	14	23895271	CA	C	0.998
336	14	23889373	C	A	0.998
337	11	47365154	G	A	0.998
338	14	23884226	C	T	0.998
339	14	23896793	C	G	0.998
340	14	23886076	C	T	0.998
341	11	47355233	C	G	0.997
342	11	47359026	C	T	0.997
343	14	23893192	T	A	0.997
344	14	23895254	C	T	0.997
345	11	47364284	C	T	0.997
346	11	47362770	C	T	0.997
347	11	47369219	TC	T	0.997
348	14	23886203	T	G	0.997
349	14	23884389	C	T	0.997
350	14	23884460	T	A	0.997
351	14	23886180	T	C	0.997
352	14	23887458	G	A	0.997
353	14	23892760	T	A	0.997
354	14	23902887	AC	A	0.997
355	11	47361331	C	A	0.997
356	14	23884890	G	T	0.997
357	14	23894942	C	G	0.997
358	14	23899776	G	T	0.997
359	14	23887610	C	G	0.997
360	14	23889430	T	A	0.997
361	14	23894557	G	A	0.997
362	14	23889316	C	T	0.997
363	11	47363584	T	A	0.997
364	11	47365113	C	T	0.997
365	14	23898993	C	T	0.997
366	11	47354512	C	T	0.997
367	11	47355305	T	C	0.997
368	14	23889235	G	A	0.997
369	11	47367845	G	A	0.997
370	14	23901717	T	A	0.997
371	11	47353637	C	T	0.997
372	11	47354497	G	A	0.997
373	14	23884930	G	A	0.997
374	11	47354482	C	T	0.997
375	14	23891387	A	C	0.997
376	14	23893360	T	C	0.997
377	11	47363543	G	A	0.997

378	14	23886746	G	A	0.997
379	11	47371324	C	A	0.997
380	14	23885350	G	A	0.997
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382	14	23901068	C	T	0.997
383	14	23882997	G	A	0.997
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385	14	23899843	C	T	0.997
386	11	47355529	G	A	0.997
387	11	47355234	G	A	0.997
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394	11	47361268	TA	T	0.997
395	11	47359032	C	G	0.997
396	14	23897726	T	A	0.996
397	14	23886878	C	T	0.996
398	14	23884589	C	T	0.996
399	11	47353429	G	A	0.996
400	14	23894085	G	A	0.996

U.S. Naval Academy Human Research Protection Program
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MEMORANDUM 20 Apr 2018

From: Ms. Erin Johnson, Academy's HRPP Office

To: MIDN John Joseph Brough, Chemistry Department

Subj: APPROVAL OF HUMAN SUBJECT RESEARCH

Ref: (a) SECNAVINST 3900.39D
(b) 32 CFR 219
(c) USNA HRPP Policy Manual

USNA Assurance # DoD N-40052 HRPP Approval # **USNA.2018.0030-IR-EM2-A**

1. The Superintendent, as the Institutional Official (IO), approved your research protocol "Attitudes of Genetic Screening in Military Populations" involving human subjects. It was determined to be exempt under 32 CFR 219.101(b)(2).

2. Research which is determined to be exempt under 32 CFR 219.101 is exempt from all regulatory requirements, unless there is a substantive change that could potentially alter the assessment of the exempt status. If there is a substantive change you must submit an amendment to your protocol in sufficient time to process the revisions and secure approval from the Superintendent. On an annual basis, a status update of all exempt studies will be conducted.

3. When the research has concluded, notify the USNA HRPP Office. In accordance with Section XIII of the USNA HRPP Policy and Procedures manual, provide this office with copies of any articles or presentations resulting from this research. Additionally, any presentations or publications must include acknowledgement of IRB approval using the HRPP approval number.

4. If you have any questions, please contact this office at 410-293-2533 or HRPPoffice @usna.edu

ERIN JOHNSON
Academy's HRPP Office

DEPARTMENT OF THE NAVY
UNITED STATES NAVAL ACADEMY
121 BLAKE ROAD
ANNAPOLIS MARYLAND 21402-1300

3900
28 Mar 18

MEMORANDUM

From: Chair, Institutional Review Board (Code 28)
To: Superintendent, U.S. Naval Academy

Subj: HUMAN SUBJECT RESEARCH BY MIDN JOHN JOSEPH BROUGH, CHEMISTRY DEPARTMENT

Ref: (a) SECNAVINST 3900.39E
(b) 32 CFR 219
(c) USNA HRPP Policy Manual

Encl: (1) Protocol Package for MIDN Joseph Brough (Forms 1, 3, 4, 5, 5A, CITI, and Supplemental Information)

1. Per references (a) through (c), I have reviewed the research protocol submitted by MIDN Joseph Brough from the Chemistry Department titled "Attitudes of Genetic Screening in Military Populations." The co-investigator is Dr. Melonie Teichert from the Chemistry Department.

2. The purpose of this research is to investigate the attitudes that individuals in the military have regarding genetic testing for disease. The recruitment emails and survey are included in supplemental information.

3. This research is determined to be exempt under 32 CFR 219.101(b)(2). Research which is determined to be exempt under 32 CFR 219.101 is exempt from all regulatory requirements. If there is a substantive change that could potentially alter the assessment of the exempt status, then please contact the USNA HRPP Office. On an annual basis, a status update of all exempt studies will be conducted.

Michael R. Kellermann 28 MAR 18
MICHAEL R. KELLERMANN

Date: 4/13/18

☑ Approved ☐ Modification ☐ Disapproved

Comments:

W. E. CARTER, JR
Vice Admiral, U.S. Navy
Superintendent

Attitudes of Genetic Screening in Military Populations

* Required

Genetic testing to identify individuals with increased risk to develop disease is becoming more and more available. We are interested in your thoughts about its implementation in the military. Please read the case example below to achieve a greater understanding of situations that genetic testing may be of use. Following your review of the case example, please answer the questions within the survey providing your anonymous opinions. Your completion of the survey will be taken as your consent to participate in the study.

A 20 year old, seemingly healthy male received genetic counseling for Long QT syndrome, a hereditary disorder that may cause sudden cardiac death. He received counseling and the offer of genetic testing due to the recent identification of a disease causing mutation in the LQTS1 gene in his Father following several episodes of fainting. In the presence of this mutation, people have a 40% chance of experiencing sudden cardiac death, so knowing if a person carries such a mutation may allow prevention of sudden cardiac death through treatments such as an implantable defibrillator. However, some may have concerns about knowing such information due to the anxiety it may bring, the chance insurance companies or employers may use the data against them, or other reasons.

1. **Have you ever been in the military? ***
Mark only one oval.

- ◯ Yes
- ◯ No

2. **Years of Military Service (include ROTC/service academy) ***

_____

3. **Do you have any military service outisde of ROTC/Service Academy? ***
Mark only one oval.

- ◯ Yes
- ◯ No
- ◯ N/A

4. **Have you been through the process of a medical waiver for any medical condition you have had? ***

Mark only one oval.

- ◯ Yes
- ◯ No
- ◯ Prefer not to Answer

5. **Have you or a family member ever had a medical condition thought to be genetic/inherited? ***

Mark only one oval.

- ◯ Yes
- ◯ No
- ◯ Prefer Not to Answer

6. **Gender ***

Mark only one oval.

- ◯ Female
- ◯ Male
- ◯ Other: _____

7. **How much have you read or heard about genetic testing for inherited disease?**

Mark only one oval.

- ◯ Almost Nothing
- ◯ Relatively Little
- ◯ A Fair Amount
- ◯ A Lot

8. **Here are some reasons some people give for wanting to be genetically tested. Please indicate how important each reason is for you. ***

Mark only one oval per row.

	Not at all important	Somewhat important	Very Important	Does Not Apply
To learn about my risk.	◯	◯	◯	◯
To learn about my children's/potential children's risk.	◯	◯	◯	◯
To know if I need to get screening tests more often.	◯	◯	◯	◯
To be reassured.	◯	◯	◯	◯
To make important medical decisions.	◯	◯	◯	◯

9. **Which of these reasons would be your MOST important reason for WANTING to be tested?**
Mark only one oval.

- ◯ To learn about my risk.
- ◯ To learn about my children's/potential children's risk.
- ◯ To know if I need to get screening tests more often.
- ◯ To be reassured.
- ◯ To make important medical decisions.

10. **Here are some reasons people give for NOT wanting to be genetically tested. Please indicate how important each reason is for you.**
Mark only one oval per row.

	Not at all important	Somewhat important	Very Important	Does not apply
I am concerned about the effect it would have on my family.	◯	◯	◯	◯
I do not trust modern medicine.	◯	◯	◯	◯
I believe that there is nothing that can be done to prevent genetic disease.	◯	◯	◯	◯
I am concerned that I could not handle it emotionally.	◯	◯	◯	◯
I am worried about losing my insurance.	◯	◯	◯	◯
I am worried about losing my job.	◯	◯	◯	◯
My chances of having genetic disease are small.	◯	◯	◯	◯

11. **Which of these would be your MOST important reason for NOT WANTING to be genetically tested?**
Mark only one oval.

- ◯ I am concerned about the effect it would have on my family.
- ◯ I do not trust modern medicine.
- ◯ I believe that there is nothing that can be done to prevent genetic disease.
- ◯ I am concerned that I could not handle it emotionally.
- ◯ I am worried about losing my insurance.
- ◯ I am worried about losing my job.
- ◯ My chances of having genetic disease are small.

For the next nine responses, please indicate if you strongly agree, agree, disagree, strongly disagree, or take a neutral position in regard to the given statement.

12. **I am curious about my disposition to develop genetic disease. ***

Mark only one oval.

- ◯ Strongly Agree
- ◯ Agree
- ◯ Neutral
- ◯ Disagree
- ◯ Strongly Disagree

13. **I would have my newborn child genetically tested to learn which diseases they may develop in adulthood. ***

Mark only one oval.

- ◯ Strongly Agree
- ◯ Agree
- ◯ Neutral
- ◯ Disagree
- ◯ Strongly Disagree

14. **I would want to know if I had a genetic condition that is treatable. ***

Mark only one oval.

- ◯ Strongly Agree
- ◯ Agree
- ◯ Neutral
- ◯ Disagree
- ◯ Strongly Disagree

15. **I would want to know if I had a genetic condition that currently has no effective treatment or cure.**

Mark only one oval.

- ◯ Strongly agree
- ◯ Agree
- ◯ Neutral
- ◯ Disagree
- ◯ Strongly disagree

16. **A person identified with genetic risk of disease should be disqualified from military service or reassigned to a different position. ***
Mark only one oval.

- ◯ Strongly Agree
- ◯ Agree
- ◯ Neutral
- ◯ Disagree
- ◯ Strongly Disagree

17. **I am worried that if I were to have genetic testing, the results may not stay confidential. ***
Mark only one oval.

- ◯ Strongly Agree
- ◯ Agree
- ◯ Neutral
- ◯ Disagree
- ◯ Strongly Disagree

18. **A Navy F/A-18 pilot has undergone genetic testing and is found to have a genetic variant with a 40% chance of causing sudden cardiac death over 5 years. This individual should be prevented from piloting aircraft.**
Mark only one oval.

- ◯ Strongly Agree
- ◯ Agree
- ◯ Neutral
- ◯ Disagree
- ◯ Strongly Disagree

19. **A Navy F/A-18 pilot has undergone routine, non-genetic blood pressure and cholesterol testing. The tests indicate that there is a 40% chance of cardiac arrest over the next 5 years. This individual should be prevented from piloting aircraft.**
Mark only one oval.

- ◯ Strongly Agree
- ◯ Agree
- ◯ Neutral
- ◯ Disagree
- ◯ Strongly Disagree

In most cases, genetic testing does not predict exact certainty of developing disease. In other words, testing may result in varying percentages that a person will or will not develop a disease. For

example, a genetic test may predict that a person has a 50% chance of developing sudden cardiac death.

20. **In your opinion, what level of risk to develop the disease makes genetic testing useful? ***
Mark only one oval.

- ◯ Less than 25%
- ◯ 25%-49%
- ◯ 50%-74%
- ◯ 74%-99%
- ◯ 100%
- ◯ Genetic testing should not be used regardless

21. **In your opinion, what level of risk to develop the disease should an individual be considered for military disqualification or reassignment for medical reasons based on a genetic test? ***
Mark only one oval.

- ◯ Less than 25%
- ◯ 25%-49%
- ◯ 50%-74%
- ◯ 75%-99%
- ◯ 100%
- ◯ An individual should not be considered for disqualification from military service based off of any genetic test

Powered by Google Forms

Attachment #1: Survey Recruitment Email

Subject: Your Participation Requested -Research

Military Members of the Naval Academy,

Your participation is requested in a Midshipman Research survey that assesses attitudes in the military related to medical testing in the military. The survey will take approximately 10 minutes to fill out and is in support of a Trident Scholar Research Project. This work has been approved by the HRPP office and Superintendent (approval number XXXX). This survey is completely anonymous. All responses are confidential and participation is voluntary.

You can access the survey by clicking the link below:
<LINK TO SURVEY>

Questions about the project may be directed to:

Midshipmen 1/C Joseph Brough
m180624@usna.edu

Thank you very much for your participation in this research!

Very Respectfully,

J Joseph Brough
MIDN USN